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Highlights

- A model with environmental, contagious, and a new opportunistic transmission mode
- Two strains of the same pathogen with different transmission modes are possible
- The model is sensitive to certain parameter changes, proper parameters are necessary
- Can be used for modelling short and long term decisions for mastitis control
A strain-, cow-, and herd-specific bio-economic simulation model of intramammary infections in dairy cattle herds

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Abstract

Intramammary infections (IMI) in dairy cattle lead to economic losses for farmers, both through reduced milk production and disease control measures. We present the first strain-, cow- and herd-specific bio-economic simulation model of intramammary infections in a dairy cattle herd. The model can be used to investigate the cost-effectiveness of different prevention and control strategies against IMI. The objective of this study was to describe a transmission framework, which simulates spread of IMI causing pathogens through different transmission modes. These include the traditional contagious and environmental spread and a new opportunistic transmission mode. In addition, the within-herd transmission dynamics of IMI causing pathogens were studied. Sensitivity analysis was conducted to investigate the influence of input parameters on model predictions. The results show that the model is able to represent various within-herd levels of IMI prevalence, depending on the simulated pathogens and their parameter settings. The parameters can be adjusted to include different combinations of IMI causing pathogens at different prevalence levels, representing herd-specific situations. The model is most sensitive to varying the transmission

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rate parameters and the strain-specific recovery rates from IMI. It can be used for investigating both short term operational and long term strategic decisions for the prevention and control of IMI in dairy cattle herds.

Keywords: mastitis, mathematical model, cow-specific, pathogen-specific

1. Introduction

Mastitis or intramammary infection (IMI) is one of the most frequent and costly diseases in dairy herds, where costs arise from both milk loss and control measures (Seegers et al., 2003; Halasa et al., 2007). They can be caused by many different pathogens, traditionally differentiated into environmental and contagious. Contagious pathogens are thought to be transmitted during the milking process (Harmon, 1994). They can cause outbreaks, infecting many animals in a short period of time resulting in high incidence rates (Zadoks et al., 2001a). In contrast, environmental pathogens are considered to be transmitted, among other things, through reservoirs in the stable and to have an endemic nature, associated with low incidence rates (Zadoks et al., 2001a; Blowey and Edmondson, 2010).

Traditionally, *Staphylococcus aureus* and *Streptococcus agalactiae* are examples for contagious pathogens, while *Escherichia coli* and *Streptococcus uberis* are considered as environmental. However, Zadoks et al. (2001a) described how *S. uberis* caused an outbreak like situation, suggesting that this particular pathogen strain was transmitted contagiously, indicating that different strains can have different properties. Consequently, control strategies should take the differences (in spread and recovery following treatment) between strains of the same pathogen species into account to be effective. Moreover, some pathogen strains may create reservoirs in the environment and yet express contagious transmission between cows, reflecting an “opportunistic” behavior that combines both contagious and environmental characteristics (Jorgensen et al., 2016). In order to capture this more differentiated behavior, we introduce a new transmission mode with both contagious and environmental characteristics at the same
time, in contrast to a purely contagious or purely environmental transmission. In the model *S. agalactiae* is used as an example for the opportunistic nature of IMI causing pathogens.

Simulation models of IMI have previously been used to investigate the impact of different management strategies against IMI (e.g. Allore et al., 1998; Halasa et al., 2010; Hagnestam-Nielsen and Østergaard, 2009; Østergaard et al., 2005; Steeneveld et al., 2011; van den Borne et al., 2010a). Some of these models have been pathogen-specific, taking traditional transmission modes between pathogens into account (Halasa et al., 2009a, 2010). Others were cow-specific, taking risk factors for infection into account (Allore et al., 1998), or focusing on characteristics of the single cow (Steeneveld et al., 2011), or herd-specific, looking into differences between herds such as herds having different pathogens (Østergaard et al., 2005). However, to our knowledge, no previous models have been simultaneously strain-, cow- and herd-specific. The model we propose considers the spread dynamics not only on species level, but also specifically distinguishes between different strains of the same species, for instance allowing future economic assessment of strain-specific diagnostics, perhaps on farm level. It includes the characteristics of the single cow for infection, recovery following potential treatment, and its future production potential, allowing a comparison of a cow to its herd mates, while modelling IMI transmission on quarter level. This allows investigating cost-effectiveness of control actions on quarter level, such as blinding (drying off) chronically infected quarters. In addition, the model includes differences between herds such as size, production and management. It is thus strain-, cow- and herd-specific and can be used as a tool to examine both short and long term decisions to prevent and control IMI for individual cows in individual herds, which is to our knowledge not available in previous bio-economic models.

The objective of this study is to describe a new transmission framework of IMI causing pathogens, including a new opportunistic transmission mode.
2. Materials and methods

2.1. Model framework

This study was conducted with the MiCull model (Mastitis-iCull), version 1.0. The model framework was created by combining an extension of the transmission framework for IMI created by Halasa et al. (2009a) with the iCull simulation model of a dairy herd described by Kirkeby et al. (2016), using R version 3.2.2 – “Fire Safety” (R Core Team, 2015).

The base iCull model is a stochastic mechanistic bio-economic model that simulates a dairy herd using single-day time steps to allow for both operational and strategic decision making (Kirkeby et al., 2016). In brief, the model simulates a dairy cattle herd in five different physical herd compartments: calves, heifers, lactating cows, dry cows and calving area. Each cow spends a random (drawn from a given distribution) predefined number of days in each compartment before moving on to the next, with the exception of possible removal from the herd by culling or slaughter decisions (see 2.3). Lactation curves and somatic cell count (SCC) curves are modelled for every cow and depend on cow-specific parameters, indicating the individual level relative to the mean in the herd (Græsbøll et al., 2016). Feeding is dependent on the life stage of each animal, and for lactating cows it is modelled based on the amount of milk produced (Kirkeby et al., 2016).

In the present MiCull model, lactation and SCC curves, as well as farmer decisions, were adjusted to include IMI related factors as described below. The transmission framework for IMI includes environmental (constant infection probability), contagious (infection probability depends on the number of infected quarters), and opportunistic (infection probability depends on the number of infected quarters or the presence of bacteria in the environment) transmission on quarter level, cow-specific infection and recovery, and different strains of the same pathogen.
2.2. Pathogen transmission

Pathogen transmission occurs on quarter level, i.e. between the quarters of dairy cows in a herd, independent of whether two quarters belong to the same or different cows. Each quarter can be in one of three infection states: susceptible (S), subclinically infected (I_s), and clinically infected (I_c), or it can be blinded (NA). At the moment, the model includes 5 different pathogen strains for demonstration purposes (Table 1). Other pathogens or updated pathogen parameters can be easily added. New infections with IMI causing pathogens are handled differently for milking cows, dry cows and heifers as described below.

2.2.1. Susceptibility

The MiCull model is cow-specific, including in the infection process in lactating cows. Risk factors, such as parity and previous cases of clinical IMI (quarter-level), are used to adjust the susceptibility for IMI of a cow (Zadoks et al., 2001b). Cows in their first parity and quarters without prior IMI are taken as reference, and the risk ratios for cows in the second and third or higher parity (\(RR^{(\text{parity})}\)), as well as for quarters with prior infections (\(RR^{(\text{prior})}\)) are calculated (mean of \(S.\ aureus\) and \(S.\ uberis\), Zadoks et al., 2001b). The product of all risk ratios pertaining to a quarter \(q\) is then used to adjust the susceptibility \(\text{Susc}_q\) of the quarter for new IMI, \(\text{Susc}_q = RR_q^{(\text{parity})} \cdot RR_q^{(\text{prior})}\). In equation (1), the susceptibility leads to an adjustment of the transmission rate, depending on cow parameters, thus leading to cow-specific infection.

2.2.2. Lactating cows

For lactating cows, all transitions between the three infection states are modelled (Figure 1). The probability of infection for each quarter includes the susceptibility and is thus cow-specific.

In the model, all pathogen strains are identified by a unique strain ID (strain), and active pathogens are marked as such. Infections can occur for all active strains, and the respective infection probabilities \(p_q^{(\text{strain})}\) are calculated for all quarters \(q\) every day/time step, depending on the transmission...
mode, see equation (1). In the equation, all parameters except the susceptibility factor $Susc_q$ (see 2.2.1) and the total number of quarters $N$ depend on the pathogen strain, which is not specifically notated in (1) for easier readability, it will however be noted in the text (e.g., $\beta^{\text{strain}}$ instead of $\beta$).

\[
p_q^{\text{strain}} = \begin{cases} 
1 - \exp(-\beta \cdot \sum_{d} \cdot d^{-1} \cdot t_i) & \text{(environmental),} \\
1 - \exp(-\beta \cdot \frac{1}{N} \cdot \sum_{d} \cdot d^{-1} \cdot t_i) & \text{(opportunist)} \\
1 - \exp(-\beta \cdot \frac{1}{N} \cdot \sum_{d} \cdot d^{-1} \cdot t_i + \theta) & \text{(contagious),} \\
1 - \exp(-\beta \cdot \frac{1}{N} \cdot \sum_{d} \cdot d^{-1} \cdot t_i + \theta) & \text{(opportunist).} 
\end{cases}
\]

(1)

$\beta^{\text{strain}}$ is the transmission rate of that pathogen strain. For environmental strains, the infection probabilities only depend on the respective transmission rates. $I^{\text{strain}} = I_S^{\text{strain}} + I_C^{\text{strain}}$ (see Figure 1) is the number of quarters (in lactating cows) already infected with a specific pathogen strain at the beginning of the current time step $t_0$. A higher number of infected quarters $I^{\text{strain}}$, increases the infection probability for contagious and opportunistic strains. $I_i^{\text{strain}}$ is the number of quarters that were infected with a strain...
at the end of time step \(t_0 - i\). It is taken into account in the environmental part of opportunistic transmission, where the pathogen strain decays in the environment for \(d_{\text{strain}}\) days until 1% of the initial bacteria remain and then disappear. The environmental share is given by \(\varepsilon_{\text{strain}}\), while \(\eta_{\text{strain}}\) is an additional scaling factor for the infectiousness of the strain’s environmental part compared to its contagious part. \(\theta_{\text{strain}}\), representing a purely environmental factor (e.g., introduction by humans), allows (re)infection with a strain that is not present in the cows nor the environment of the herd. All parameter values can be found in Table 1.

The probabilities \(P_q^{(\text{strain})}\) of the active pathogens are combined by

\[
P_q^{(\text{total})} = 1 - \prod (1 - P_q^{(\text{strain})}),
\]

and each previously uninfected quarter gets infected with this probability. The infecting pathogens are then drawn according to their relative risk. Infected quarters are allocated to \(I_{S_{\text{strain}}}^{(\text{strain})}\) or \(I_{C_{\text{strain}}}^{(\text{strain})}\) depending on the probability \(P_c^{(\text{strain})}\) (Table 1).

At each new time step, previously subclinically infected quarters in \(I_S\) have the chance to flare up or spontaneously recover (Figure 1) with a certain pathogen-specific probability (Table 1). The clinically infected quarters are subjected to a three day treatment (default) with antibiotics, they will thereafter either recover or persist as subclinical cases (remission) (Figure 1). The probability for recovery depends on the causative pathogen and is cow-specific, according to Steeneveld et al. (2011) (Table 1 shows the base probability).

The model includes the possibility to scale transmission rate, flare up probability, and spontaneous recovery probability by any factor, and to replace the probability \(P_c^{(\text{pathogen})}\) that a new infection will be clinical by another value.

2.2.3. Dry cows

For dry cows, IMI will generally be or stay subclinical, except in the first or last week of the dry period, where clinical IMI can also occur.
<table>
<thead>
<tr>
<th>Parameter Description</th>
<th>Pathogen</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission rate ($\beta$)</td>
<td>Rate for susceptible animals entering subclinical or clinical state</td>
<td>$S. aureus$</td>
<td>0.0179*</td>
</tr>
<tr>
<td></td>
<td>$S. agalactiae$</td>
<td>0.0086*</td>
<td>Leelaphongpatoon et al. (2016)</td>
</tr>
<tr>
<td></td>
<td>$S. uberis$ (contagious)</td>
<td>0.0155*</td>
<td>Zadoks et al. (2001a)</td>
</tr>
<tr>
<td></td>
<td>$S. uberis$ (environmental)</td>
<td>0.0155*</td>
<td>Zadoks et al. (2001a)</td>
</tr>
<tr>
<td></td>
<td>$E. coli$</td>
<td>0.0004*</td>
<td>Barkema et al. (1998)</td>
</tr>
<tr>
<td>Probability of clinical state ($P_c$)</td>
<td>Probability of entering clinical state when infected</td>
<td>$S. aureus$</td>
<td>0.17</td>
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<tr>
<td></td>
<td>$S. agalactiae$</td>
<td>0.01*</td>
<td>Zadoks et al. (2003)</td>
</tr>
<tr>
<td></td>
<td>$S. uberis$ (contagious)</td>
<td>0.32</td>
<td>Zadoks et al. (2003)</td>
</tr>
<tr>
<td></td>
<td>$S. uberis$ (environmental)</td>
<td>0.32</td>
<td>Zadoks et al. (2003)</td>
</tr>
<tr>
<td></td>
<td>$E. coli$</td>
<td>0.65</td>
<td>Hooper and Smith (2003)</td>
</tr>
<tr>
<td>Flare up probability</td>
<td>Probability of subclinical animals going to clinical state</td>
<td>$S. aureus$</td>
<td>0.0064*</td>
</tr>
<tr>
<td></td>
<td>$S. agalactiae$</td>
<td>0.0005*</td>
<td>Zadoks et al. (2005b)</td>
</tr>
<tr>
<td></td>
<td>$S. uberis$ (contagious)</td>
<td>0.0068*</td>
<td>Zadoks et al. (2005b)</td>
</tr>
<tr>
<td></td>
<td>$S. uberis$ (environmental)</td>
<td>0.0068*</td>
<td>Zadoks et al. (2005b)</td>
</tr>
<tr>
<td></td>
<td>$E. coli$</td>
<td>0.0005*</td>
<td>Döpfer et al. (1999)</td>
</tr>
<tr>
<td>Spontaneous recovery probability</td>
<td>Base probability of spontaneous cure for subclinical animals</td>
<td>$S. aureus$</td>
<td>0.0064*</td>
</tr>
<tr>
<td></td>
<td>$S. agalactiae$</td>
<td>0.0023*</td>
<td>Leelaphongpatoon et al. (2016)</td>
</tr>
<tr>
<td></td>
<td>$S. uberis$ (contagious)</td>
<td>0.0143*</td>
<td>van den Borne et al. (2010b)</td>
</tr>
<tr>
<td></td>
<td>$S. uberis$ (environmental)</td>
<td>0.0143*</td>
<td>van den Borne et al. (2010b)</td>
</tr>
<tr>
<td></td>
<td>$E. coli$</td>
<td>0.0221*</td>
<td>van den Borne et al. (2010b)</td>
</tr>
<tr>
<td>Recovery probability</td>
<td>Probability of recovery for clinical animals that are treated</td>
<td>$S. aureus$</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>$S. agalactiae$</td>
<td>0.7</td>
<td>Steeneveld et al. (2011)**</td>
</tr>
<tr>
<td></td>
<td>$S. uberis$ (contagious)</td>
<td>0.7</td>
<td>Steeneveld et al. (2011)</td>
</tr>
<tr>
<td></td>
<td>$S. uberis$ (environmental)</td>
<td>0.7</td>
<td>Steeneveld et al. (2011)</td>
</tr>
<tr>
<td></td>
<td>$E. coli$</td>
<td>0.8</td>
<td>Steeneveld et al. (2011)</td>
</tr>
<tr>
<td>$\varepsilon$</td>
<td>Environmental share in opportunistic transmission</td>
<td>$S. agalactiae$</td>
<td>0.1</td>
</tr>
<tr>
<td>$\eta$</td>
<td>Scaling factor for infectiousness of environmental part in opportunistic transmission</td>
<td>$S. agalactiae$</td>
<td>1</td>
</tr>
<tr>
<td>$\theta$</td>
<td>Purely environmental factor in opportunistic transmission</td>
<td>$S. agalactiae$</td>
<td>0</td>
</tr>
<tr>
<td>$d$</td>
<td>Number of days the bacteria survive in the environment</td>
<td>$S. agalactiae$</td>
<td>40</td>
</tr>
</tbody>
</table>

* rounded values

** $S. aureus$ values were adjusted by the factor by which incidence is different in Barkema et al. (1998).

*** used value of *Streptococcus dysgalactiae* or *uberis*

Table 1: Rates and probabilities used in the transmission framework for lactating cows (Figure 1). All parameters are implemented in daily time steps for all quarters.
New infections in dry cows can occur for every active strain. Contagious strains are considered active, if at least one quarter of one cow in the herd is infected with that particular strain. Similarly, opportunistic strains are considered active, if they are still present in the herd or if they have a non-zero purely environmental element $\theta^{(\text{strain})}$. This is important, as the probability of infection is calculated according to

$$p^{(\text{strain})} = 1 - \exp\left(-\beta^{(\text{dct,strain})}\right)$$

for every active pathogen strain, where $\beta^{(\text{dry,strain})}$ is depending on both the pathogen and whether the cow was treated with dry cow therapy or not (Table 2). Note that the infection probability in the dry period is the same for all quarters and not cow-specific. The probabilities of the active pathogens are combined by (2). Each previously uninfected quarter gets infected with this probability. The infecting pathogens are then drawn according to their relative risk. Infected quarters are allocated to $I^{(\text{strain})}_S$ or, if the cow is in the first or last week of the dry period, to $I^{(\text{strain})}_C$ depending on the probability $P^{(\text{strain})}_{c,\text{dry}}$ (Table 2).

Similar to lactating cows, subclinically infected quarters in dry cows can flare up or spontaneously recover (Table 2), however flare up can only happen in the first or last week of the dry period.

Additionally, a cow with a flared up quarter in the first week after dry off will receive dry cow treatment. Dry cow quarters change their status from $I_C$ to $I_S$ or $S$ after the same number of days as for clinical cases in lactating cows. Here, dry cow treatment influences the probability of recovery for the clinical quarter (Table 2). For clinical quarters in the last week of the dry period, the probability for recovery is calculated similarly as for lactating cows, only without regarding somatic cell count (SCC) and days in milk.

As for lactating cows, transmission rate, flare up probability, and spontaneous recovery probability can be scaled and the probability $I^{(\text{strain})}_{c,\text{dry}}$ that a new infection will be clinical can be replaced.
### Table 2: Rates and probabilities used in the transmission framework for dry cows (Figure 1)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Pathogen</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission rate ($\beta_{\text{dry}}$)</td>
<td>Rate for susceptible animals entering subclinical or clinical state</td>
<td>S. aureus</td>
<td>0.0079*</td>
<td>Halasa et al. (2010)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S. agalactiae</td>
<td>0.0011***</td>
<td>Halasa et al. (2010)</td>
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<td></td>
<td></td>
<td>S. uberis (contagious)</td>
<td>0.0011*</td>
<td>Halasa et al. (2010, 2009c)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S. uberis (environmental)</td>
<td>0.0011*</td>
<td>Halasa et al. (2010, 2009c)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E. coli</td>
<td>0.0002*</td>
<td></td>
</tr>
<tr>
<td>Transmission rate ($\beta_{\text{dct},\text{dry}}$)</td>
<td>Rate for susceptible animals with dry cow treatment entering subclinical or clinical state</td>
<td>S. aureus</td>
<td>0.0005*</td>
<td>Halasa et al. (2010, 2009c)</td>
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<td>Halasa et al. (2010, 2009c)</td>
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<td>E. coli</td>
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<td></td>
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<tr>
<td>Probability of clinical state ($P_c$)</td>
<td>Probability of entering clinical state when infected</td>
<td>S. aureus</td>
<td>0.1</td>
<td>Halasa et al. (2010)</td>
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<td></td>
<td>S. agalactiae</td>
<td>0.1</td>
<td>Halasa et al. (2010)</td>
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<td>S. uberis (contagious)</td>
<td>0.1</td>
<td>Halasa et al. (2010)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S. uberis (environmental)</td>
<td>0.1</td>
<td>Halasa et al. (2010)</td>
</tr>
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<td></td>
<td></td>
<td>E. coli</td>
<td>0.1</td>
<td>Halasa et al. (2010)</td>
</tr>
<tr>
<td>Flare up probability</td>
<td>Probability of subclinical animals going to clinical state</td>
<td>S. aureus</td>
<td>0.006*</td>
<td>Halasa et al. (2010)</td>
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<td>Halasa et al. (2010)</td>
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<td>Spontaneous recovery probability</td>
<td>Probability of spontaneous cure for subclinical animals</td>
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<td>0.0079*</td>
<td>Halasa et al. (2010)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S. agalactiae</td>
<td>0.0086*</td>
<td>Halasa et al. (2010)</td>
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<td>Halasa et al. (2010)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E. coli</td>
<td>0.0221*</td>
<td>Halasa et al. (2010)</td>
</tr>
<tr>
<td>Recovery probability</td>
<td>Probability of recovery for clinical animals with dry cow treatment</td>
<td>S. aureus</td>
<td>0.77</td>
<td>Halasa et al. (2010, 2009b)</td>
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<tr>
<td></td>
<td></td>
<td>S. agalactiae</td>
<td>0.89</td>
<td>Halasa et al. (2010, 2009b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S. uberis (contagious)</td>
<td>0.89</td>
<td>Halasa et al. (2010, 2009b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S. uberis (environmental)</td>
<td>0.89</td>
<td>Halasa et al. (2010, 2009b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E. coli</td>
<td>0.9</td>
<td>Halasa et al. (2010, 2009b)</td>
</tr>
</tbody>
</table>

* rounded values
** same value as during lactation
*** value of Streptococcus spp.

Table 2. Rates and probabilities used in the transmission framework for dry cows (Figure 1), probability of clinical state, flare up and spontaneous recovery were taken from Halasa et al. (2010), who recalculated them from Bradley and Green (2004) and Green et al. (2005). All parameters are implemented in daily time steps, for all quarters.
2.2.4. Heifers

Currently, there is no dynamic pathogen transmission in heifers, i.e. cows prior to their first calving. Instead, each pathogen strain has a certain probability to infect heifers (Table 2). These probabilities are added up for the active pathogens to a total probability for heifers to be assigned to $I_S$ one day before calving. The pathogens are then drawn depending on their part of the total probability.

2.3. Production effects and economy

2.3.1. Feeding

Cows are often fed roughage as basic feed plus concentrate to facilitate a higher milk production. To our knowledge, no studies have explicitly estimated the decrease in feed due to IMI. In this model, the feed usage per lactating cow is a function of the energy-corrected milk (ECM) produced, corresponding to €0.1852 per ECM (following Kirkeby et al., 2016). Therefore, cows with subclinical and clinical IMI automatically have a decreased feed intake because their milk production is decreased, as described below in sections 2.3.3 and 2.3.4. The model also includes an additional option to simulate a farmer who feeds only roughage without concentrate to cows that have their milk withdrawn due to antibiotic treatment, as described in Halasa et al. (2009a). For those cases, a proportion of the feed costs is subtracted to account for lower concentrate usage. By default, however, this option is disabled.

2.3.2. Milking

The daily milk yield is calculated for lactating cows (Kirkeby et al., 2016). However, differing from the iCull model, the income from milk is now dependent on the fat and protein content. Using the data set described in Kirkeby et al. (2016), we estimated the daily mean protein percentage for all cows, depending on days in milk (DIM) and parity (1, 2 and 3+), and fitted a three parameter Wood curve to each cow and parity in the data set (see Græsbøll et al., 2016). Based on the same data set, we estimated distributions for the fat to protein...
ratio per parity. In the simulation model, each cow is assigned three parameters for the Wood curve to describe the protein percentage and, for each simulated day, the protein content is calculated based on the cow’s DIM. A fat to protein ratio is then drawn from the respective distribution for each cow and used to calculate the daily fat yield based on the milk yield and protein percentage.

The income from milk is given by summing the income from fat and protein, withdrawing a milk handling fee based on the daily kg milk yield and multiplying with a penalty or bonus factor, depending on the bulk tank SCC (Table 3).

2.3.3. Subclinical IMI

Subclinically infected animals are subject to an increased SCC. For every subclinical quarter, an increase in the SCC is added to the generic simulated SCC, according to Schepers et al. (1997, Table 1) and Wilson et al. (1997, Table 2, used for scaling missing pathogens). If more than one quarter of a cow is subclinically infected, the maximum increase is added; however, the SCC is cut off at a maximum of 10,000,000 as higher SCC values are rarely observed and for numeric stabilization. The increased SCC in these subclinically infected animals also leads to a higher bulk tank SCC, which is calculated as the weighted mean SCC in the total daily amount of milk produced. The milk price, in turn, is dependent on the bulk tank SCC, as a bulk tank SCC up to 200,000 will result in a 4% bonus, while a bulk tank SCC above 500,000 will result in the maximal penalty of 10% (see Kirkeby et al., 2016).

Linked to an increased SCC in subclinically infected cows is milk loss, and as the SCC varies daily for each cow, so does the milk loss. We used the estimates given in Hortet et al. (1999) to reduce the milk yield of each cow with at least one subclinical quarter according to SCC, DIM (except for primiparous cows) and parity (primiparous or multiparous, where we used the estimates for parity 1 or 3+, cows, respectively), see supplementary Figure S7. The milk loss per cow is restricted to 2kg, which corresponds to the maximal loss in parity 3+ within the limits of Hortet et al. (1999).
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic treatment period</td>
<td>3</td>
<td>Number of days in antibiotic treatment, milk from treated cows is discarded.</td>
<td>Steeneveld et al. (2011)</td>
</tr>
<tr>
<td>Milk withdrawal period</td>
<td>6</td>
<td>Number of days after antibiotic treatment where the milk from treated cows is discarded.</td>
<td>van den Borne et al. (2010a), Michael Farre pers. comm.</td>
</tr>
<tr>
<td>Acute mastitis probability</td>
<td>0.01</td>
<td>Probability for a cow to get acute mastitis, when it gets clinical mastitis.</td>
<td>Michael Farre pers. comm.</td>
</tr>
<tr>
<td>Antibiotic treatment cost</td>
<td>€33.3</td>
<td>Cost for antibiotic treatment of one cow, not including vet visit or farmer labor.</td>
<td>Michael Farre pers. comm.</td>
</tr>
<tr>
<td>Dry cow therapy cost</td>
<td>€9.6</td>
<td>Cost for dry cow therapy for one cow, which includes teat sealants in 20% of the cases.</td>
<td>Michael Farre pers. comm.</td>
</tr>
<tr>
<td>Opportunity costs</td>
<td>€20</td>
<td>Opportunity costs for treatment of one cow with clinical mastitis.</td>
<td>Halasa et al. (2009a), Michael Farre pers. comm.</td>
</tr>
<tr>
<td>Protein price</td>
<td>€5.8132</td>
<td>Price for 1 kg protein</td>
<td><a href="http://www.arla.dk">www.arla.dk</a>, September 2017</td>
</tr>
<tr>
<td>Fat price</td>
<td>€4.1519</td>
<td>Price for 1 kg protein</td>
<td><a href="http://www.arla.dk">www.arla.dk</a>, September 2017</td>
</tr>
<tr>
<td>Milk handling fee</td>
<td>€0.0001343</td>
<td>Fee for handling 1 kg milk</td>
<td><a href="http://www.arla.dk">www.arla.dk</a>, September 2017</td>
</tr>
<tr>
<td>Culling costs</td>
<td>ca. €500</td>
<td>Costs for culling one cow (price of a new heifer minus slaughter value)</td>
<td>Huijps et al. (2008)</td>
</tr>
</tbody>
</table>

Table 3: Model parameters related to IMI treatment, culling, and milk price.
2.3.4. Clinical IMI

Clinical mastitis can reduce a cow’s milk production even after the cow is not clinical anymore (Gröhn et al., 2004). We used Gröhn et al. (2004) estimates for milk loss following clinical infection to fit logarithmic functions to the amount of milk lost for each pathogen type and for primiparous and multiparous cows. As a logarithmic function did not seem to be a suitable fit for primiparous cows with clinical IMI caused by *Streptococcus* spp., we fitted in this case a linear function truncated at zero (Figure S9). The respective milk loss is added throughout the whole lactation to the cow’s produced milk, starting on the first day of clinical infection. An example of the milk loss is given in Figure S8.

When a cow gets a clinical IMI, it is treated. In the model, the default option comprises three days of antibiotic treatment, during which and for six days afterwards the cow’s milk is withdrawn and discarded (Table 3). Treatment costs are based on expert opinion on Danish herds (see Table 3) and are comparable to the numbers given in Halasa et al. (2009a). They are divided into the costs of the antibiotics (€33.3) and opportunity costs (€20), which include the time the farmer has to spend on cows with clinical IMI (Table 3).

2.3.5. Dry cow therapy

Dry cow therapy is the treatment of cows with long lasting antibiotics at dry off. In the model, the default option applies antibiotic treatment only to cows that get a clinical IMI during the first week of dry off to study the dynamics of IMI without the influence of specific dry cow management. Other options include different selection strategies for selective dry cow therapy: cows with a history of clinical IMI, cows with a high SCC at the last monthly milk yield recording, cows with either of those options, and blanket dry cow therapy.

2.3.6. Culling

In the model, culling happens on a weekly basis. If there are more than 200 lactating cows, the farmer will cull the excess number of cows. About half of the culled cows are chosen randomly, those are the cases that have to
be culled e.g. because of lameness. The others are chosen by the farmer from a culling list, where (s)he prioritizes the animals for culling, e.g. cows with production in the bottom 20%, with insemination difficulties, or with a high SCC at the last monthly milk yield recording, by applying weights for every unfavorable circumstance to each cow (Kirkeby et al., 2016). For every high SCC (> 200,000) at subsequent monthly milk yield recordings, the respective cows will be increasingly prioritized, with a low SCC resetting this prioritization. After 12 months with a continuously high SCC, cows will be culled at the first possibility, though the default value of 12 months can be easily changed to reflect different management strategies.

As subclinical IMI causes an increase in the SCC, cows with subclinical IMI have a higher probability to be prioritized for culling because of a high SCC. Cows with previous clinical IMI also have a higher probability of being chosen for culling than their herd mates. Bar et al. (2008a) found that the odds ratios for primiparous cows being culled were 7.46, 16.12 and 20.08, if they had 1, 2 or ≥ 3 clinical mastitis cases, respectively (exponentiating values of Table 4 in Bar et al. (2008a)); for multiparous cows the respective odds ratios were 3.74, 5.00 and 6.36. We used these values to apply weights to the culling decision made by the farmer, with multiparous cows with one previous clinical IMI receiving a weight of 1 and the other mentioned cases receiving weights scaled to reflect the ratios found in Bar et al. (2008a). Furthermore, it can happen, that a cow gets flagged for an acute IMI when it becomes clinical (Table 3). These cows will be put on top of the culling list, from which the farmer chooses in the weekly culling.

Prioritization for culling is therefore: involuntary cases, cows with acute IMI, cows with a continuously high SCC, cows with the highest weight for culling.

The costs of culled animals are calculated as the costs for raising a replacement heifer for each cow that is culled (to two years of age, €510), minus the slaughter value the farmer gets for the culled cow (€51).
2.3.7. Model outputs

The epidemiological model output consists of daily cow level prevalences, as well as the total number of flare ups, remissions, subclinical, and clinical IMI for each simulation. Furthermore, it includes the total number of culled cows due to acute IMI, subclinical IMI and a history of clinical IMI. Culling due to subclinical IMI includes all culled cows with at least one subclinically infected quarter that were prioritized for culling because of a high SCC. To avoid counting a culled cow several times, culling due to the cow having a history of clinical IMI includes only cases in which the cow did not have a high SCC at the last monthly milk yield recording. Cows culled because of acute IMI are counted separately.

The economical model output includes the total milk loss in kg due to subclinical or clinical IMI (both milk loss and withdrawal), as well as the total income from milk and the mean milk price penalty percentage (see sections 2.3.2, 2.3.3, and 2.3.4). As the fat and protein percentages for lost milk are not calculated, a mean milk price of around €0.4099 per kg is used to calculate costs for milk loss (mean Arla milk price in September 2017). The mean milk price penalty value together with the total income from milk is used to calculate the possible penalty paid due to a high bulk tank SCC. Further economic output includes expenses for treatment of clinical IMI as described above (2.3.4), as well as costs for dry cow therapy (Table 3).

2.4. Model validation

Several methods for internal validation were used on the model (Sargent, 2003). Rationalism, including operational graphics: various scenarios were compared to check consistency and credibility of model outputs. Traces: single cows were traced over time to check for consistency. Face validity: model assumptions and outputs were evaluated by mastitis experts. External validation was conducted by comparing model predictions to the literature, as data to validate such a complicated model is not available.
2.4.1. Model convergence

We tested model convergence on two parameters by simulating 1000 iterations. In a scenario without any IMI causing pathogens, we tested convergence of the energy corrected milk yield (ECM), and in a scenario with three pathogens (using default parameters taken from literature, see Table 1), we tested convergence on the number of clinical cases. In both cases visual inspection showed that 500 iterations were sufficient to obtain stable results (Figure S6). Further visual inspections showed that after five simulated years herd, population, and transmission dynamics were always stable, warranting a five year burn-in period.

2.4.2. Sensitivity analysis and model runs

We performed sensitivity analysis on a herd with 200 cows, using 500 simulations of 5 years, with a burn-in time of an additional 5 years. All scenarios were initiated with a 20% starting prevalence for all pathogen strains, with the exception of environmental strains in multiple pathogen scenarios, where the starting prevalence was set to 10%. These values are arbitrary and were chosen only for presentation of the model.

Sensitivity analyses were carried out on the transmission rate ($\beta$), the spontaneous recovery probability, the probability that a newly infected animal becomes a clinical IMI case ($P_c$), the flare up probabilities, the environmental part of the opportunistic pathogen ($\varepsilon$), and the number of days the opportunistic pathogen can survive in the environment ($d$). For the transmission rate parameter, various scaling factors (all $<1$, except for E. coli where factors $>1$ were considered) were considered in the sensitivity analysis; selected values are presented in Table 4. Sensitivity analysis for the spontaneous recovery probability consisted of several scaling factors between 0.25 and 2. For the other parameters, sensitivity analyses focused on the actual value instead of the scaling factor: $P_c$ and flare up probability were varied between 0.01 and 0.85 and between 0.0002 and 0.02, respectively. The parameter $\varepsilon$ in opportunistic transmission was varied between 0 and 1, while $d$ was reduced down to 10 days in increments of 5 days.

To obtain insight into how the model would simulate the dynamics of pathogen
spread, a great number of scenarios were run in the sensitivity analyses, of which only a few with different transmission rates were selected and presented here. In the supplementary material, more scenarios were included.

3. Results

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Pathogens</th>
<th>Transmission rate</th>
<th>Transmission rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>scaling factor</td>
<td>(dry cows)</td>
</tr>
<tr>
<td>7</td>
<td><em>S. aureus</em></td>
<td>0.2</td>
<td>0.0036</td>
</tr>
<tr>
<td>9</td>
<td><em>S. aureus</em></td>
<td>0.1</td>
<td>0.0018</td>
</tr>
<tr>
<td>14</td>
<td><em>E. coli</em></td>
<td>0.55</td>
<td>0.0037</td>
</tr>
<tr>
<td>21</td>
<td><em>E. coli</em> (contagious)</td>
<td>0.8</td>
<td>0.0124</td>
</tr>
<tr>
<td>49</td>
<td><em>S. aureus</em></td>
<td>0.25</td>
<td>0.0045</td>
</tr>
<tr>
<td></td>
<td><em>S. agalactiae</em></td>
<td>0.5</td>
<td>0.0078</td>
</tr>
<tr>
<td>56</td>
<td><em>S. agalactiae</em></td>
<td>0.25</td>
<td>0.0078</td>
</tr>
<tr>
<td></td>
<td><em>S. aureus</em> (contagious)</td>
<td>0.5</td>
<td>0.0078</td>
</tr>
<tr>
<td>68</td>
<td><em>S. agalactiae</em></td>
<td>0.5</td>
<td>0.0078</td>
</tr>
<tr>
<td></td>
<td><em>S. agalactiae</em> (contagious)</td>
<td>0.5</td>
<td>0.0078</td>
</tr>
<tr>
<td>88</td>
<td><em>S. agalactiae</em> (environmental)</td>
<td>0.01</td>
<td>0.0002</td>
</tr>
<tr>
<td>98</td>
<td><em>S. aureus</em></td>
<td>0.25</td>
<td>0.0045</td>
</tr>
<tr>
<td></td>
<td><em>S. agalactiae</em></td>
<td>0.5</td>
<td>0.0078</td>
</tr>
<tr>
<td></td>
<td><em>S. agalactiae</em> (environmental)</td>
<td>0.01</td>
<td>0.0092</td>
</tr>
<tr>
<td></td>
<td><em>E. coli</em></td>
<td></td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table 4: Selected scenarios. All pathogens start with a 20% prevalence, except in the five pathogen scenario (98), where the environmental strains start with a 10% prevalence. Transmission rates are rounded.

Figure 2: Cow level prevalences in one pathogen scenarios 7, 9, 14, and 21, see Table 4. Every scenario shows smoothed daily prevalences for each of 500 iterations over 5 years with a 5 year burn-in period (with one random iteration displayed in gray), as well as the mean daily prevalence (bold, black). The bottom lines show the daily prevalences of clinical IMI, with the mean displayed as a dashed line.
Figure 3: Cow level prevalences in two pathogen scenarios 49, 56, 68, and 88, see Table 4. Every scenario shows smoothed daily prevalences for each of 500 iterations over 5 years after a 5 year burn-in period (with one random iteration displayed in gray), as well as the mean daily prevalence (bold, black). The bottom lines show the daily prevalences of clinical IMI, with the mean displayed as a dashed line.

Figure 4: Cow level prevalences in the five pathogen scenario see Table 4, scenario 98. It shows the smoothed daily prevalences for each of 500 iterations over 5 years after a 5 year burn-in period (with one random iteration displayed in gray), as well as the mean daily prevalence (bold, black). The bottom lines show the daily prevalences of clinical IMI, with the mean displayed as a dashed line.

The methods used for internal validation showed valid and consistent outcomes of the model in all scenarios. As an illustration, nine scenarios were selected. These include four one pathogen scenarios for different pathogens, four two pathogen scenarios with different pathogen combinations, and one five pathogen scenario with all pathogens (Table 4). Scenarios where exact literature values were used as transmission parameters, led to high prevalences in our setting (results not shown). Therefore, the selected scenarios used adjusted transmission rates, leading to more realistic prevalence estimates (Figures 2, 3, and 4).
Figure 2 shows selected scenarios with one active pathogen. The starting prevalence is set to 20%, and during the burn-in period it fluctuates depending on the pathogen strain (i.e. the combination of all transmission parameters, see scenarios 7, 14, and 21, Figure 2), or changes depending on the transmission rate (scenarios 9 and 7, Figure 2). After the burn-in period, the prevalence has reached a mostly stable level.

The model also allows coexistence of multiple pathogens or strains, regardless of their transmission mode, on different prevalence levels, depending on the scaling of the transmission parameters (Figures 3 and 4). Scenario 49 and 56 show two pathogen scenarios, where the active pathogen strains are *S. aureus* and *S. agalactiae* or a contagious *S. uberis*, respectively. The transmission rate for *S. aureus* is the same in both scenarios, however the mean daily prevalence is higher in scenario 56, where the second active pathogen is present at a low level.

In scenario 68, *S. agalactiae* and the contagious *S. uberis* strain are coexisting at similar levels to scenario 49 and 56, respectively. Scenario 88 (Figure 3) shows another scenario with two active pathogen strains, in this case a contagious and an environmental strain of *S. uberis*. Both strains are present at a similar prevalence, with a higher variation for the contagious strain.

Scenario 98 shows a five pathogen, which also includes both a contagious and an environmental strain of *S. uberis* together with contagious *S. aureus*, environmental *E. coli*, and opportunistic *S. agalactiae* (Figure 4). The contagious strains have the same transmission rate as in the two pathogen scenarios and are at similar daily prevalence levels. The opportunistic *S. agalactiae* strain also has the same transmission rate as in the two pathogen scenarios, but the prevalence level has increased.

The epidemiological output in Table 5 shows the number of quarter cases per year (median over 500 iterations and mean over 5 years simulation period); in the multiple pathogen scenarios, numbers are summed over all pathogens. The number of subclinical IMI includes all remission cases, while the number of clinical IMI includes all flare up cases. Also, one cow may be counted more than one time for the same infection, e.g. if a clinical quarter went into remission and
Table 5: Epidemiological output in median number (with 5% and 95% percentiles) of quarter cases per year (mean over 5 years) of the scenarios in Table 4. Numbers are rounded.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Flare up</th>
<th>Remission</th>
<th>subclinical IMI</th>
<th>clinical IMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>120 (101, 140)</td>
<td>113 (95, 134)</td>
<td>258 (228, 293)</td>
<td>134 (113, 157)</td>
</tr>
<tr>
<td>9</td>
<td>44 (36, 53)</td>
<td>40 (32, 48)</td>
<td>98 (84, 112)</td>
<td>47 (38, 57)</td>
</tr>
<tr>
<td>14</td>
<td>7 (4, 10)</td>
<td>4 (2, 6)</td>
<td>77 (51, 107)</td>
<td>8 (5, 12)</td>
</tr>
<tr>
<td>21</td>
<td>78 (57, 114)</td>
<td>72 (49, 110)</td>
<td>244 (174, 363)</td>
<td>149 (105, 225)</td>
</tr>
<tr>
<td>49</td>
<td>172 (147, 200)</td>
<td>164 (138, 192)</td>
<td>436 (385, 498)</td>
<td>196 (167, 227)</td>
</tr>
<tr>
<td>56</td>
<td>221 (197, 257)</td>
<td>209 (186, 247)</td>
<td>482 (437, 551)</td>
<td>264 (237, 306)</td>
</tr>
<tr>
<td>68</td>
<td>33 (27, 40)</td>
<td>22 (17, 28)</td>
<td>139 (112, 171)</td>
<td>46 (38, 56)</td>
</tr>
<tr>
<td>88</td>
<td>58 (50, 67)</td>
<td>45 (37, 53)</td>
<td>136 (120, 156)</td>
<td>94 (82, 108)</td>
</tr>
<tr>
<td>98</td>
<td>261 (232, 294)</td>
<td>250 (221, 284)</td>
<td>693 (640, 752)</td>
<td>370 (333, 410)</td>
</tr>
</tbody>
</table>

Table 6: Median number (with 5% and 95% percentiles) of culled cases per year (mean over 5 years) of the scenarios in Table 4, see section 2.3.6 for culling categories. Numbers are rounded.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>high SCC</th>
<th>acute IMI</th>
<th>history of IMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>22 (18, 26)</td>
<td>1 (0, 2)</td>
<td>3 (2, 4)</td>
</tr>
<tr>
<td>9</td>
<td>13 (10, 16)</td>
<td>0 (0, 1)</td>
<td>2 (1, 3)</td>
</tr>
<tr>
<td>14</td>
<td>24 (19, 29)</td>
<td>0 (0, 0)</td>
<td>0 (0, 1)</td>
</tr>
<tr>
<td>21</td>
<td>15 (10, 20)</td>
<td>1 (0, 3)</td>
<td>4 (3, 6)</td>
</tr>
<tr>
<td>49</td>
<td>48 (41, 55)</td>
<td>1 (1, 2)</td>
<td>2 (1, 3)</td>
</tr>
<tr>
<td>56</td>
<td>35 (30, 39)</td>
<td>2 (1, 3)</td>
<td>3 (2, 4)</td>
</tr>
<tr>
<td>68</td>
<td>27 (21, 33)</td>
<td>0 (0, 1)</td>
<td>2 (1, 3)</td>
</tr>
<tr>
<td>88</td>
<td>10 (7, 13)</td>
<td>1 (0, 3)</td>
<td>5 (3, 6)</td>
</tr>
<tr>
<td>98</td>
<td>68 (60, 76)</td>
<td>2 (1, 3)</td>
<td>2 (1, 4)</td>
</tr>
</tbody>
</table>

flared up again afterwards. For *S. agalactiae*, most clinical IMI are flared up subclinical cases and there are few clinical IMI, if the prevalence is at moderate levels (scenario 14). In contrast, the contagious *S. uberis* strain leads to many more clinical cases, both flared up and directly infected (scenario 21).

Table 6 shows the number of culled cows per year (median over 500 iterations and mean over 5 years simulation period); acutely culled cows, subclinical cows that were culled with a noticeable high SCC, and culled cows with a history of clinical IMI. Most cows that are culled because of IMI related reasons are connected to a high SCC, though the number and proportion of cows culled with subclinical IMI or a history of clinical IMI also depends on the causative pathogen.

The costs associated with subclinical and clinical IMI can be found in the supplementary Tables S1, S2, and S3.
Further sensitivity analyses showed that the probability of spontaneous recovery for subclinical cases is similarly influential on the prevalence as the transmission rate (Figure S1): with a higher probability of spontaneous recovery, the prevalence decreases.

Sensitivity analysis for the probability for a newly infected quarter to be clinical ($P_c$, Table 1) showed that for *S. agalactiae* and the contagious strain of *S. uberis* an increased proportion of clinical cases leads to a decreased prevalence, while this effect was less observable in the environmental pathogens and *S. aureus* (Figure S2). Similarly, the higher the flare up probability is, the lower the prevalence becomes (Figure S3).

If the environmental part $\varepsilon$ in the opportunistic infection is increased, the prevalence increases, too, ranging from a mean of 17.8% with pure contagious infection ($\varepsilon = 0$) to a mean of 30.3 without any contagious part ($\varepsilon = 1$) after 10 years. This effect is not visible, if the prevalence is low (< 5%, Figure S4).

Reducing the number of days $d$ the opportunistic pathogen can survive in the environment showed marginal effects on model outcome, which is expected due to how the bacterial survival is weighted.

4. Discussion

The described model simulates a dairy cattle herd on daily basis, including the spread of IMI causing pathogens within the herd. It also includes various treatment variants for IMI, that will be investigated for cost-effectiveness in following studies. The aim of this study was to describe the model, including a new opportunistic transmission mode. With the historical view of purely contagious and purely environmental pathogens being questioned (e.g., Zadoks et al., 2001a; Jørgensen et al., 2016), we think that this feature is an important step in modelling IMI spread, representing both the possibility of strain specific transmission properties and recent suggestions of *S. agalactiae*’s potential opportunistic behaviour. The opportunistic transmission mode combines both contagious (via milking) and environmental transmission in one strain, as indi-
cated by Jorgensen et al. (2016). The contagious part of this new feature was
transferred from previously already implemented contagious transmission (Ha-
lasa et al., 2009a). The environmental part represents the decay of the pathogen
in the environment over time. Using an exponential function to represent the
decay of infectious agents in the environment is not unusual, although slope
of decline may differ for different pathogens (e.g., Whiting et al., 1996; Halasa
et al., 2016). Still, implementing it for *S. agalactiae* should be acceptable. The
infection probability depends on three main elements, in addition to the ba-
sic transmission rate; the contribution of the environment, the slope of decay,
and the duration of pathogen survival in the environment. The latter has been
approximated based on literature (Jorgensen et al., 2016), but the two other
elements are lacking actual data from the field. We speculate that the impact of
the environmental part is strain-specific, meaning that some strains are mainly
found in the environment, persisting there for some time and causing new infec-
tions, while others mainly spread via the contagious route. The weight of each
mechanism is unknown, which warrants further research to assess the influence
of the environment on the spread of this pathogen. Our model allows weighting
of the contagious and environmental parts of pathogen spread, depending on,
e.g., the strain type. Our current parameterization ($\varepsilon = 0.1$) would represent a
mainly contagious spread of the pathogen with occasional transmission of IMI
through the environment. This was done as an illustration of opportunistic
spread in the model. In the future, the effect of the different parameters must
be examined properly, when simulating the impact of control strategies against
IMI caused by *S. agalactiae*.

Default values for all transmission parameters were taken from literature
(Tables 1 and 2), which led to unrealistically high prevalences (Figures 2, 3,
and 4). This is not surprising, as studies are usually conducted in herds with
large problems or even outbreaks with the specific pathogens. In those herds,
pathogen spread, and thereby the calculated transmission rates, are high. On
top of that, our additional susceptibility factor $\text{Susc}_q$, used to re-scale the trans-
mission rates to include cow-specific infection, leads to higher infection proba-
bilities in the model. The estimated transmission rates from the literature do
not consider quarter factors, but instead they are average values for all quar-
ters. For instance, it is known that the risk of infection is higher for quarters
with previous IMI (Zadoks et al., 2001b). In order to consider the effect of
these factors in the estimation of infection probability, the transmission rates
are multiplied by the relative risks of quarter factors (the susceptibility factor),
and hence the probability becomes artificially higher than normal. To represent
a realistic situation, it therefore becomes important to rescale the transmission
rates, as the quarter factors should be taken into account at the same time.
Future studies estimating transmission rates should consider the effects of quar-
ter and cow factors on the transmission rate, if possible, in order to be able to
accurately model spread dynamics of IMI causing pathogens.

Our results show sensitivity of the prevalence to changes in transmission rate
and other transmission parameters (see Figures S1–S4), making the use of the
right parameters important. It is therefore worrisome that estimates of trans-
mission rates are scarce and limited to few studies from few herds (e.g., Zadoks
et al., 2001a, 2003; Barlow et al., 2013; Leelahapongsathon et al., 2016). Nev-
evertheless, we decided to include a susceptibility factor and thereby cow-specific
transmission in the model and adjust transmission, as studies have shown that
relevant risk factors exist (e.g., Zadoks et al., 2001b). As these factors may be
pertinent for management decisions regarding IMI, not including them would
prevent investigating cow-specific management strategies in the future. Further-
more, as IMI causing pathogens are thought to be transmitted, among other
things, during the milking process (Harmon, 1994) or through reservoirs in the
environment (Zadoks et al., 2001a; Blowey and Edmondson, 2010), transmis-
sion rates are dependent on herd related factors. Considering that there are
only few studies estimating these rates, and conditions are prone to change over
the years, transmission rates, in the absence of proper data, will have to be
adjusted in some way to model different IMI situations representing different
herds or management systems. Hopefully, future research can close these gaps.

Another point regarding transmission is the assumption in the model that
the same transmission rate can be used for transmission to quarters of the same
cow or of other cows. When transmission happens through the milking equip-
ment, for instance, fluctuations in the milking vacuum could, depending on
the milking machine’s claw, lead to a reflux of milk from an infected quarter
into uninfected teats (Besier et al., 2016). IMI can also be transmitted by flies
(Owens et al., 1998). A fly would probably land on a quarter of the same cow
before flying away, possibly leading to a higher risk of within cow spread. Given
the absence of proper data to parameterize this process, the made assumption
seems inevitable. Should this knowledge gap be closed in the future, differ-
ent transmission probabilities could be used for within cow and between cow
transmission.

Our results showed expected behavior when parameters were changed in
sensitivity analyses. Different scenarios showed different prevalence patterns,
e.g., in scenarios 49 and 56 (Figure 3), where the prevalence of *S. aureus* was
higher when the second pathogen’s prevalence was lower. In scenario 98 (Figure
4), *S. agalactiae* reached a higher prevalence level than in scenarios 49 or 68
(Figure 3), even though the transmission rate was the same, showing a different
behavior of opportunistic transmission depending on the prevalence of other
IMI pathogens. An increased total prevalence leads to more quarters having a
higher risk of contracting an IMI, as history of IMI is modelled as a risk factor
for new IMI. This, combined with the fact that *S. agalactiae* can build up and
persist in the environment, leads to its increased incidence. The model can
thus simulate different transmission behaviors of pathogens and different herds,
which is necessary to investigate, e.g., how effective a treatment regimen is under
different circumstances. The economic part of the model yields comparable
results to other models. For instance, Steeneveld et al. (2007) found an average
per case cost of €109 for subclinical IMI, while our scenario 9 resulted in a
median cost of about €100 per subclinical IMI case S1. In the same scenario,
the median cost for a clinical IMI case was around €226, which is similar to
other studies by e.g. Halasa et al. (2009a) (€101 to €328), Huijps et al. (2008)
(€164 to €235), and Bar et al. (2008b) (€179 on average). As a substantial
part of the costs for IMI arises from culling (Tables S1 and S2), and farmers behave differently in terms of culling (e.g., Fetrow et al., 2006), modelling herd-specific scenarios instead of average herds is also important for cost-effectiveness analyses.

Altogether, our model is able to simulate strain-, cow-, and herd-specific transmission of IMI causing pathogens on quarter level and with a daily time step. It also includes the possibility to consider different farmer priorities concerning culling by changing culling weights, or to include a prediction of the future value of a cow relative to its herd mates (Græsbøll et al., 2017) in the culling decision of the farmer, allowing a potentially more economic choice of cows to be culled. Moreover, the necessary features to study several treatment strategies for clinical IMI and selection strategies for dry cow therapy are already implemented in the model, and further strategies or pathogen strains can be easily added. This makes it possible to simulate specific herds and investigate the cost-effectiveness of various changes to management/prevention or treatment/control strategies, both short term (operational decision making) and long term (strategic decision making), that can also be strain- and cow-specific.

As different changes may be more cost-effective depending on the herd, and selective treatment decisions may be more effective when selecting the right cows to treat, it is important to include strain-, cow-, and herd-specifics in a model investigating cost-effective strategies. Simulating specific instead of average herds also means simulating diverse herd-specific disease situations, that are represented by different combinations of pathogens at different (stable) prevalence levels, which is possible with this model as shown in Figures 3 and 4.

Other bio-economic models simulating mastitis and mastitis control already exist, but to our knowledge none of the existing models combine all features presented in this model. The model by Halasa et al. (2009a, 2010) used the same transmission framework on cow instead of quarter level, but without including cow-specific infection and recovery. By simulating on quarter level, we allow multiple infections per cow, as this happens in reality, though one quarter can still only be infected by one pathogen or strain in our model. With this, our
The model also differs from e.g. the SIMMAST model (Allore et al., 1998), which also simulates on cow level, though it does not include cow-specific recovery, and only allows infection with one pathogen at a time. The SimHerd model (Østergaard et al., 2005) allows several pathogens per cow and is cow- and herd-specific, however, cow-specific factors are only considered for infection. SimHerd's mastitis framework is based on weekly time steps and infection through a baseline risk function for all mastitis pathogens. While this is a valid approach in the setting Østergaard et al. (2005) investigated, our model can explore both constant spread and infection over time, as well as transitions between the two. In addition, modelling on quarter level is closer to the underlying biology, as IMI occurs on quarter level. By modelling the actual biological unit, IMI management can also be modelled on quarter level, e.g. drying off chronically infected quarters.

While previous models may distinguish between contagious and environmental spread, our model explicitly allows both contagious and environmental strains of the same pathogen, exemplified by S. uberis, and also introduces a new third opportunistic transmission type with both contagious and environmental properties, as discussed above. Furthermore, while we only included S. uberis with an environmental and a contagious strain to illustrate the possibility of having two strains with different transmission modes, this option should be kept in mind regarding other pathogens like e.g. S. aureus, as the model allows easy addition of other pathogens or pathogen strains. The question of which type of transmission is the right one for a particular pathogen strain cannot be answered by models, but our model allows the user to choose between the three mentioned transmission types and compare e.g. management strategies, depending on what kind of transmission is assumed for a strain. This allows investigations into cost-effectiveness of various strain-, cow-, and herd-specific IMI prevention and control measures, while including a farmer’s current strategies, thereby hopefully making it easier to convince farmers to adopt proposed cost-effective changes in the future.
5. Conclusions

We developed a strain-, cow-, and herd-specific bio-economic simulation model of IMI and introduced a new opportunistic transmission mode. The model is sensitive to parameter changes in the transmission framework, but it can be fitted to simulate various pathogen scenarios, representing different herd situations. However, we found that available parameter estimations for IMI transmission or cure may be becoming outdated and we therefore suggest future studies to investigate new parameter estimations. The economic output allows cost estimations of both subclinical and clinical IMI, which lie within the ranges found in earlier studies. This makes it possible to use the model in future studies to investigate cost-effective prevention and control measures against IMI that are tailored to a specific herd, hopefully making it easier to convince the farmer to adopt proposed changes.

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References


Østergaard, S., Chagunda, M. G. G., Friggens, N. C., Bennedsgaard, T. W.,
Klaas, I. C., 2005. A stochastic model simulating pathogen-specific mastitis

Role of horn flies (Haematobia irritans) in staphylococcus aureus-induced masti-
titis in dairy heifers. American Journal of Veterinary Research 59 (9), 1122–
1124.

R Core Team, 2015. R: A Language and Environment for Statistical Computing,
R Foundation for Statistical Computing, Vienna, Austria.
URL https://www.R-project.org/

Sargent, R. G., 2003. Verification and validation of simulation models. Proceed-

Schepers, A. J., Lam, T. J. G. M., Schukken, Y. H., Wilmink, J. B. M.,
cell counts to determine thresholds for uninfected quarters. Journal of Dairy
Science 80 (8), 1833–1840.

mastitis and mastitis economics in dairy cattle herds. Veterinary Research
34 (5), 475–491.

Steeneveld, W., Swinkels, J., Hogeveen, H., 2007. Stochastic modelling to as-
 sess economic effects of treatment of chronic subclinical mastitis caused by

Steeneveld, W., van Werven, T., Barkema, H. W., Hogeveen, H., 2011. Cow-
specific treatment of clinical mastitis: An economic approach. Journal of
Dairy Science 94 (1), 174–188.

to estimate economic benefits of lactational treatment of subclinical staphy-


