Deterministic modeling of the transmission dynamics of intramammary infections

Deterministic modeling of the transmission dynamics of intramammary infections

Amira Rachah[1,a], Gunnar Dalen[2], Håvard Nørstebø[2], Olav Reksen[1], John W. Barlow[3]

[1] Norwegian University of Life Sciences, Department of Production Animal Clinical Sciences, 0033 Oslo, Norway
[2] TINE SA, P.O. box 58, N-1430 Ås, Norway
[3] Department of Animal Science, University of Vermont, Burlington VT 05405, USA

E-mail: [a]amira.rachah@nmbu.no

Abstract. We present a novel deterministic modelling approach that describes the transmission dynamics of intramammary infections (IMI) caused by *Corynebacterium* spp. (*Corynebacterium* species) in a US dairy herd. Longitudinal, quantitative, dynamic models are likely to be valuable for predicting infections outbreak risk, quantify the effectiveness of response tactics and performing response planning. In this paper, we established an approach based on SIS compartmental model subject on appropriate unknown parameters that we estimated within lactation month as time variable. Firstly, we stratified the days of study (calendar days) in several strata. Secondly, we modelled the transmission of *Corynebacterium* spp. by using lactation month (months since last calving) as time variable within each of the separate strata. We estimated the unknown parameters of the model by using a deterministic approach, based on real data fitting procedure. The real data, from which the parameters of the model are estimated, were obtained in a field trial conducted in a New York dairy herd (US).

1. Introduction

Intramammary infections (IMI), are considered the most common disease limiting the production of dairy farms worldwide. They are associated with a large economic impact and impaired animal welfare. Intramammary infections caused by bacterial infection are routinely diagnosed through bacterial milk culture [1, 2, 3]. *Corynebacterium* spp. are considered to be minor udder pathogens [4, 5].

The development of decision support tools for detection and management of IMI remains the subject of extensive research. IMI with *Corynebacterium* spp. are generally mild causing limited loss in milk production. However, significant elevation of somatic cell count (SCC) has been observed [5]. Pathogen-specific transmission patterns have been described for other major and minor mastitis pathogens [6, 7] but only recently for *Corynebacterium* spp. [8]. This has motivated us to establish a new multiphase modeling approach of the transmission dynamics of *Corynebacterium* spp. IMI by stratifying the entire days of study (calendar days) in several strata and modeling the transmission of the udder pathogen by using lactation month as time variable within each of the separate strata.

Mathematical models of infectious diseases (for animals) are powerful tools for understanding infection dynamics by providing useful predictions about the potential transmission of infections

and the effectiveness of control measures [9, 10, 11]. It is only recently that a small number of studies have integrated the principle of compartmental models to describe the dynamics of mastitis transmission and the overall effects of interventions for the modeling of infectious diseases in animals [12, 13, 14, 15, 16, 17]. In this work, a Susceptible-Infectious-Susceptible (SIS)-model is used for the modeling. The basic reproduction number, R_0, is used in compartmental transmission models for determining transmission of a disease at the population level. It is defined as the number of secondary cases that one infectious case can produce if introduced into a susceptible population [18, 19].

Modeling the progression of a disease depends on appropriate parameter values that are often unknown and must be estimated from real data. In this study, we have used a general linear model for parameter estimation. The parameters estimated were used in a deterministic state-transition model to describe the transmission dynamics of *Corynebacterium* spp. from preexisting IMI. In the traditional way of modeling, veterinarians used to do modeling of the transmission of IMI by using days of study (calendar days) as the time variable. In this study, we established a novel approach based on SIS compartmental model subject on appropriate unknown parameters that we estimated within lactation month as time variable. Firstly, we stratified the days of study (calendar days) in several strata. Secondly, we modelled the transmission of *Corynebacterium* spp. by using lactation month (months since last calving) as time variable within each of the separate strata. We estimated the unknown parameters of the SIS model by using a deterministic approach, based on real data fitting procedure. The real data, from which the parameters of the model are estimated, were obtained in a field trial conducted in a New York dairy herd (US). The likelihood of infection differs with lactation month [20]. Cows are generally more susceptible to udders infections during the first months after calving as compared to later lactation months. Traditional infectious disease models does not take into account that susceptibility to infection varies with the composition of the population. The number of cows in the most susceptible versus more resistant months of lactation will vary throughout a one year cycle. Our modelling approach attempts to take this variability into account. Therefore the main aim of this study is to develop a novel mathematical description of the transmission dynamics of *Corynebacterium* spp. IMI by using a multiphase modeling approach and optimization. The approach is based on the stratification of the entire days of study in two strata and the modeling of the transmission of *Corynebacterium* spp. by using lactation month as time variable within each of the separate strata. The optimization is used for real data fitting. Then, we wanted to compare transmission parameters and cure rates for *Corynebacterium* spp. IMI between the different strata.

2. Data collection

Data were obtained from a 13-month longitudinal observational study in one commercial dairy Holstein herd in New York, US. Details on the herd, microbial analyses and sampling framework has been published previously [7]. Mastitis control practices, including pre- and postmilking teat disinfection and the use of blanket dry-cow therapy, were standardized.

Quarter milk samples were collected for bacteriological diagnosis monthly from lactating cows. In total 371 cows were sampled, and the median number of cows sampled each month was 210. In addition, samples were collected within 3 days after parturition and whenever animals were moved to or from the lactation pen. Altogether 14401 quarter samples were analyzed from this herd. Trained field technicians collected the scheduled monthly quarter milk samples. Additional quarter milk samples were collected by farm personnel that had received training for this. All samples were collected according to recommended guidelines [2]. Samples collected monthly were kept on ice after collection and during transport to the laboratory, where they were frozen. Additional samples collected by farm personnel were frozen immediately after collection. Samples were thawed in the laboratory and bacteriological culture was performed

according to standard procedures [2]. Samples with culture results presenting more than 3 morphologically different colony types were treated as contaminated and excluded from further analyses. A quarter was considered to have an infection (IMI) with *Corynebacterium* spp. when adhering to at least one of the following criteria: 1) $\geq 1000\, c.f.u./ml$ of the pathogen was cultured from a single sample, 2) $\geq 500\, c.f.u./ml$ of the pathogen were cultured from two out of three consecutive milk samples, 3) $\geq 100\, c.f.u./ml$ were cultured from three consecutive milk samples, or 4) $\geq 100\, c.f.u./ml$ were cultured from a clinical sample, where c.f.u respresents colony-forming units [4]. Positive bacteriological culture results that did not meet any of the above criteria were classified as transient colonizations.

3. Multiphase modeling and parameters estimation

The transmission dynamics of *Corynebacterium* spp. IMI were described by Susceptible-Infectious-Susceptible (SIS)-model [8]. The model describes a population of lactating udder quarters divided into two compartments: S denotes susceptible quarters with no *Corynebacterium* spp. IMI, and I denotes quarters affected with IMI caused *Corynebacterium* spp., where the compartments represent the proportion of lactating quarters in each state. The dynamics of state transitions are illustrated in Figure 1. The model is defined by the following nonlinear ordinary differential equations (ODE):

$$\frac{dS}{dt} = -\beta SI + \alpha I + \theta_s N\mu - \mu S, \tag{1}$$

$$\frac{dI}{dt} = \beta SI - \alpha I + \theta_I N\mu - \mu I. \tag{2}$$

The interaction between the classes is quantified by the parameters α and β. The parameter β denotes the transmission of infection from a quarter with an IMI caused by *Corynebacterium* spp. to a susceptible quarter. The parameter α describes the daily rate of cured quarters. N represents the sum of susceptible and infected quarters in the study at any given time. The daily rate of entry and exit of quarters to and from the lactation compartments is described by μ. Entries of quarters from the fresh pen to the different compartments within the lactation pen are determined by the proportions θ_S and θ_I.

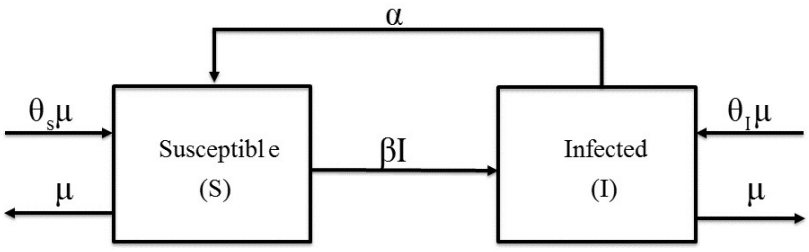

Figure 1. Diagram of the mathematical model of transmission of intramammary infections caused by with *Corynebacterium* spp.. The boxes represent the state variables and the arrows represent the flow rates between susceptible (S) and infected (I) states [8].

In a recent work on the transmission of IMI, Dalen et all [8] studied the transmission of *Corynebacterium* spp. IMI by using the calendar time as the time variable in their modeling. The calendar time is the real time of study (calendar days). The curve of infected quarters obtained from their study is presented in Figure 2.

Our multiphase modelling is based on two steps:

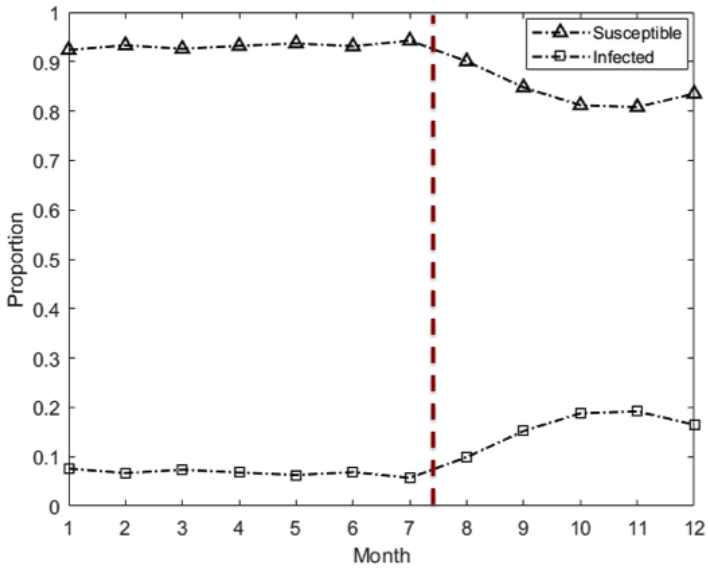

Figure 2. Transmission of *Corynebacterium* spp. without stratification: Proportion of susceptible and infected quarters throughout days study obtained from real data [8]. Dashed line is for the stratification.

- Stratification of the entire days of study (or calendar time) into several strata.
- Modeling of the transmission of *Corynebacterium* spp. by using lactation month as time variable within each of the separate strata.

In the stratification modelling, we stratify the entire study days as follow: (1) Strata 1: from month 1 until month 7; (2) Strata 2: from month 8 until month 12. An underlying assumption of transmission modelling with lactation month as time variable, is that there are no major changes of transmission dynamics within each strata. However the time period of each strata must be short enough to capture changes in infection dynamics from one time strata to the next.

The estimation of the parameters is based on real data fitting procedure using nonlinear least squares method for nonlinear ordinary differential equations (ODEs) [21, 22]. According to the definition of the least squares method, the best-fit curve of a given type is the curve that has a minimal sum of deviation squared from the real data. The mathematical description of our approach is as follow: Find estimates of the unknown parameters β, α, μ, θ_s and θ_I of the *Corynebacterium* spp. IMI model, for a given real data described by the points $(t_j, I_{\text{real},j})$, $j = 1, 2, \ldots, n$ where t_j is the time and $I_{\text{real},j}$ is the value of proportion infected at the time t_j, which will be fitted by the I-solution of the ODEs that describe the SIS model, given by $I_{\text{siml},j}$ such that the sum of the squares of the deviations between $I_{\text{real},j}$ and $I_{\text{siml},j}$ is minimized. These deviations for each data point are given by $d = I_{\text{real},j} - I_{\text{siml},j}$, $j = 1, 2, \ldots, n$ where $I_{\text{siml},j}$ is the proportion infected at the time t_j obtained from the resolution of the nonlinear ordinary equations of the *Corynebacterium* spp. model. According to the nonlinear least squares method, the best fitting curve has the property that $d_1^2 + d_2^2 + \ldots d_n^2 = \sum_{j=1}^{n} d_j^2 = \sum_{j=1}^{n} (I_{\text{real},j} - I_{\text{siml},j})^2 =$ minimum. The fitting procedure is associated with the numerical resolution of the nonlinear

ordinary differential equations of the *Corynebacterium* spp. model. Then we can formulate our mathematical approach for the estimation of parameters, as follows:

$$\begin{aligned} &\text{minimize} \quad \sum_{j=1}^{n} \left(I_{\text{real},j} - I_{\text{siml},j}\right)^2, \\ &\text{subject to} \quad \text{equations of dynamics } (1) - (2), \end{aligned} \tag{3}$$

where the unknown parameters, in this optimization problem, are β, α, μ, θ_s and θ_I.

4. Result

The proportion of infected by lactation month within strata 1 and 2 are presented respectively in Figure 3. For all strata of calendar time, the transmission of *Corynebacterium* spp. increases throughout the first 5 months (150 days) of lactation and decreases toward the end of the lactation period. This dynamics is not apparent in Figure 2.

By using real data fitting procedure using nonlinear least squares method for nonlinear ordinary differential equations (ODEs), we obtained the values of the parameters of the transmission dynamics of *Corynebacterium* spp. IMI for the two strata for the Holstein herd, as presented on the table 1. The values of β and α within the first and the second strata show the nature of the infection that is not feasible in the case of calendar time. The values of β and α within the two strata confirm the evolution of the intensity of the transmission of the infection by lactation month (Figure 3). That is also confirmed by the value of the reproductive number R_0 which was equal 0.64 in the first strata and 1.26 in the second strata.

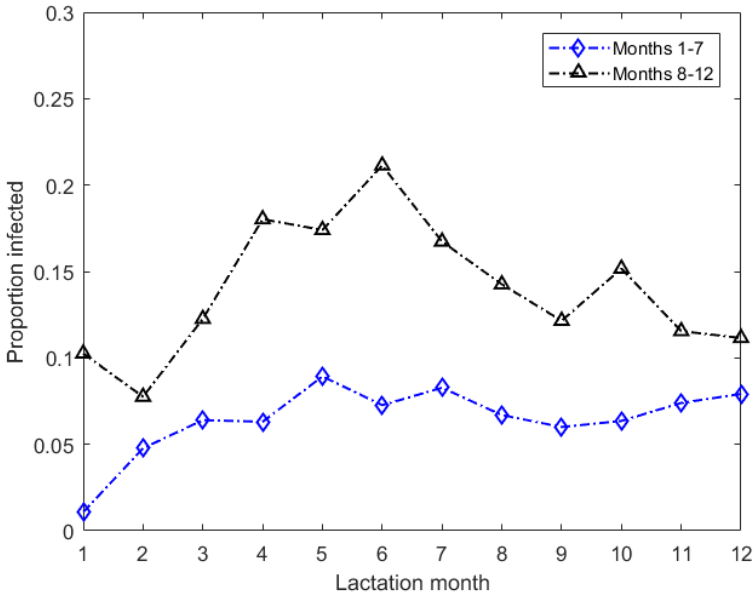

Figure 3. Transmission of *Corynebacterium* spp. with stratification: (1) Strata 1: from month 1 until month 7; (2) Strata 2: from month 8 until month 12.

Table 1. Estimation of the parameter of the SIS-model within strata 1 and strata 2.

Parameters	Strata 1	Strata 2
β	0.023	0.024
α	0.016	0.015
μ	0.02	0.004
θ_S	0.9	0.81
θ_I	0.06	0.013
$R_0 = \frac{\beta}{\mu+\alpha}$	0.64	1.26

By comparing between the parameters of the different strata (see table 1), the change in the transmission of Corynebacterium spp. is not based primarily on β and α but based importantly on change of daily rate of cows leaving and entering the lactation pen μ and the rate of entries from the fresh pen to the I compartment θ_I , that we would not reveal if we only studied the proportion of infected quarters throughout the calendar time. The value of μ decreases from 0.02 until 0.004. from the first to the second strata. The value of θ_I decreases from 0.06 until 0.013. from the first to the second strata. The pattern of a higher rate of new infections during mid lactation persists in the two strata, but with different magnitude. The figure 3 shows that the force of infections is not the same in both strata, that's confirmed by the evolution in R0 from 0.64 to 1.26 which is associated with less movements of animals in strata 2.

5. Discussion

Figure 2 shows the real infected quarters over days of study (calendar days). By modelling transmission using lactation month as time variable, we obtain data on how the transmission (new infections / cure) relates to lactation months. By using lactation month as the time variable within strata, we are able to observe whether the nature of the infection, differs between consecutive strata. E.g. it would be feasible to assume that most new infections by major pathogens happen during early lactation.

The evolution of the basic reproductive number from 0.64 to 1.26 obtained after modelling by using lactation month as time variable shows that most new infections by Corynebacterium spp. happen with different magnitude within strata 1 and strata 2 (Figure 3). By using calendar time, it is not clear that the infection happen in early lactation. The modelling by lactation month shows the prevalence in *Corynebacterium* spp. as the cow proceeds through lactation, where as the calendar time modeling shows the transmission of the infection on the population level. The important change of the daily rate of cows leaving and entering the lactation pen μ and the rate of entries from the fresh pen to the I compartment θ_I, shows that the pattern of a higher rate of new infections during mid lactation persists in the two strata, but with different magnitude.

6. Conclusion

A novel multiphase modelling of the transmission dynamics of *Corynebacterium* spp. IMI by using lactation month shows the behaviour of the infections that is not feasible in case of modelling by calendar time. By comparing between the parameters of the two strata, the change in the transmission of Corynebacterium spp. is not based only on the change of the transmission and recovered rates but an important change of daily rate of cows leaving and entering the lactation pen and the rate of entries from the fresh pen to the I compartment. Within the two strata new infections during mid lactation are detected but with different magnitude.

References

[1] Halasa T, Huijps K, Osteras O and Hogeveen H 2007 Economic effects of bovine mastitis and mastitis management *Review. Vet. Q.* **29** p 18
[2] Hogan J S, Gonzalez R N, Harmon S C, Nickerson S C, Pankey J W and Smith K L 1999 *Laboratory handbook on bovine mastitis* (Nat. Mastitis Council)
[3] Hogeveen H, Huijps K and Lam T J 2011 Economic aspects of mastitis: new developments. *N. Z. Vet. J.* **59** 16
[4] Blagitz M G, Souza F N, Santos B P, Batista C F, Parra A C, Azevedo L F, Melville P A, Benites N R and Della Libera A M 2013 Function of milk polymorphonuclear neutrophil leukocytes in bovine mammary glands infected with Corynebacterium bovis *J. Dairy Sci.* **96** 3750
[5] Brooks B W and Barnum D A 1984 Experimental colonization of the bovine teat duct with Corynebacterium bovis and the effect on milk somatic cell counts *Can. J. Comp. Med.* **48** 141
[6] Barlow J W, Zadoks R N and Schukken Y H 2013 Effect of lactation therapy on Staphylococcus aureus transmission dynamics in two commercial dairy herds *BMC Vet. Res.* **9(1)** 28
[7] Reksen O, Grohn Y T, Barlow J W and Schukken Y H 2012 Transmission dynamics of intramammary infections with coagulase-negative staphylococci *J. Dairy Sci.* **95** 4899
[8] Dalen G, Rachah A, NørstebøH, Schukken Y H, Gröhn Y T, Barlow J W and Reksen O 2018 Transmission dynamics of intramammary infections caused by Corynebacterium species *J. Dairy Sci.* **101** 472
[9] Andersen S, Dohoo I R, Olde Riekerink R and Stryhn H 2010 Mastitis Research Workers. Diagnosing intramammary infections: evaluating expert opinions on the definition of intramammary infection using conjoint analysis *J. Dairy Sci.* **93** 2966
[10] Keeling M J and Rohani P 2011 *Modeling Infectious Diseases in Humans and Animals* (New Jersey : Princeton University Press)
[11] Ogunnaike B A and Ray W H 1994 *Process dynamics, modeling, and control. Topics in chemical engineering* (Oxford University Press, New York)
[12] Allore H G and Erb H N 1999 Approaches to modeling intramammary infections in dairy cattle *Prev. Vet. Med.* **39** 279
[13] Anderson R M and May R M 1991 *Infectious diseases of humans : dynamics and control* (Oxford University Press)
[14] Lam T J 1996 Dynamics of bovine mastitis: a field study in low somatic cell count herds *Phd Thesis. Utrecht University*
[15] Watts J L, Lowery D E, Teel J F and Rossbach S 2000 Identification of Corynebacterium bovis and other coryneforms isolated from bovine mammary glands *J. Dairy Sci.* **83** 2373
[16] White L J, Lam T J, Schukken Y H, Green L E, Medley G F and Chappell M J 2006 The transmission and control of mastitis in dairy cows: a theoretical approach *Prev. Vet. Med.* **74** 67
[17] Zadoks R N, Allore H G, Hagenaars T J, Barkema H W and Schukken Y H 2002 A mathematical model of Staphylococcus aureus control in dairy herds *Epidemiol. Infect.* **129** 397
[18] Diekmann O, Heesterbeek J A and Metz J A 1990 On the definition and the computation of the basic reproduction ratio R0 in models for infectious diseases in heterogeneous populations *J. Math. Biol.* **28** 365
[19] Hethcote H W 2000 The Mathematics of Infectious Diseases. *SIAM Rev. Soc. Ind. Appl. Math.* **42** 599
[20] Breen J E, Green M J and Bradley A J 2009 Quarter and cow risk factors associated with the occurrence of clinical mastitis in dairy cows in the United Kingdom *J. Dairy Sci.* **96** 2551
[21] Bard Y 1974 *Nonlinear Parameter Estimation* (Academic Press, New York)
[22] Li Z F, Osborne M R and Prvan T 2005 Parameter estimation of ordinary differential equations *Ima. J. Numer. Anal.* **25** 264