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Multiphase modeling of intramammary infections caused by *Corynebacterium* species

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Abstract. A multiphase modeling approach that describes the transmission dynamics of intramammary infections (IMI) caused by *Corynebacterium* species in US dairy herd is presented in this paper. It is based on the stratification of the days of study (calendar days) in several strata and the modeling of the transmission of *Corynebacterium* spp. by using lactation month (months since last calving) as time variable within each of the separate strata. The real data, on which the modelling study was based, were obtained in a field trial conducted in a New York dairy herd (US).

1. Introduction

Mastitis, inflammation of the udder, is a common disease among dairy cows worldwide. It is one of the economically most important diseases in dairy farming, and affects both milk production and milk quality. Mastitis caused by bacterial infection is 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 intramammary infections (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 modeling of infectious diseases for animals, is a powerful tool 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, the approach is based on the stratification of the entire days of study in three strata and the modeling of the transmission of *Corynebacterium* spp. by using lactation month (months since last calving) as time variable within each of the separate strata. 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. Specifically, we firstly wanted to stratify the entire days of study in several strata and model the transmission of *Corynebacterium* spp. by using lactation month as time variable within each of the separate strata. Secondly, we wanted to compare transmission parameters and cure rates for *Corynebacterium* spp. IMI between the different strata.

2. Data collection and statistical analysis

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. Positive bacteriological culture results that did not meet any of the above criteria were classified as transient colonizations.

Statistical analysis was conducted using SAS. Transmission parameters (β) and cure

rates (α) were calculated using the generalized linear model approach (PROC GENMOD). *Corynebacterium* spp. IMI events in each monthly interval (I_M) as the outcome. S = Quarter-days in a susceptible udder, I = Quarter-days infected, N = Total quarter-days in each interval (lactation month), and β^* is the intercept in the equation: $\ln(I_M) = \beta^* + \ln\frac{SI}{N}$, and the transmission coefficient β is expressed as e^{β}. A log link, assumption of a negative binomial distribution, and offset $\ln\frac{SI}{N}$ [17], were used. The cure rate (α) was estimated with number of cured quarters from *Corynebacterium* spp. IMI events in each monthly interval (C_M) as the outcome. A log link, assumption of a negative binomial distribution, and offset $\ln I$ [17], were used. I = Quarter-days infected in each monthly interval (lactation month), and α is the intercept in the equation: $\ln(C_M) = \alpha + \ln I$, where C_M = Cured *Corynebacterium* spp. IMI events in each monthly interval, and the cure rate, α, is expressed as e^{α}.

The population level transmission dynamics were further evaluated by the basic reproduction number, R_0. The expression of R_0 is given by: $R_0 = \frac{\beta}{\mu+\alpha}$, where μ is the observed rate of entry and exit of quarters to and from the lactation compartment, and the inverse of the cure rate (α) is the duration of infection.

3. Multiphase modeling

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: (1) S denotes susceptible quarters with no *Corynebacterium* spp. IMI, and (2) 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. In a recent work on the transmission of IMI, Dalen

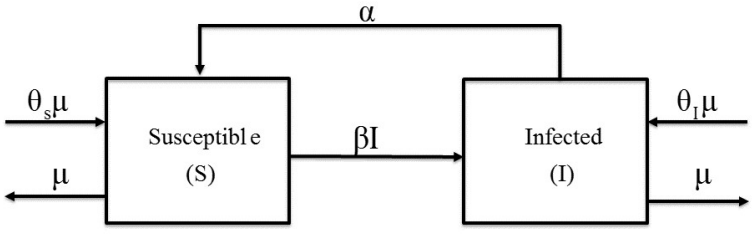

Figure 1. Diagram of the mathematical model of transmission of intramammary infections caused by with *Corynebacterium* spp.. The boxes represent the state variables and the arrows represent the flow rates between susceptible (S) and infected (I) states [8].

and 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 on Figure 2. Our

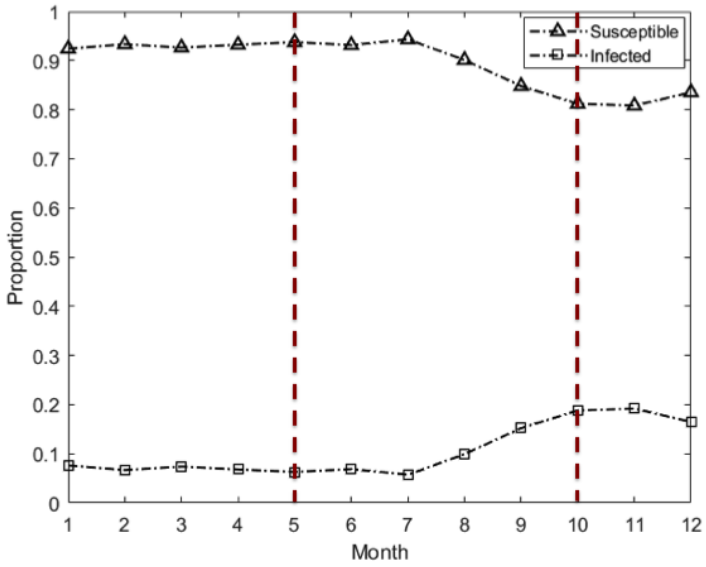

Figure 2. Transmission of *Corynebacterium* spp. without stratification: Proportion of susceptible and infected quarters throughout days study obtained from real data [8]. Dashed line is for the stratification.

multiphase modelling is based on two steps:

- 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 5; (2) Strata 2: from month 6 until month 9; (3) Strata 3: from month 10 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.

4. Result

The proportion of infected and susceptible udder quarters throughout 12 months, and the stratification of this investigation period in three strata of calendar time (1-5, 6-9 and 10-12 months) are displayed in Figure 2.

Figure 3 shows the transmission of *Corynebacterium* spp. by lactation months separately for each of the three strata of calendar time. From this figure it becomes apparent that transmission of *Corynebacterium* spp. increases throughout the first 6 months (180 days) of lactation and decreases toward the end of the lactation period for all three strata. This dynamic is not apparent when transmission is modelled by calendar time only (Figure 2)

From the statistical analysis, we obtained the values of the transmission rate β and the cure rate α as follow:

- For the first strata: The transmission rate β was 0.0187 (95%CI: 0.014-0.023) and the cure rate α was 0.0235 (95%CI: 0.018-0.029).
- For the second strata: The transmission rate β was 0.0233 (95%CI: 0.017-0.03) and the cure rate α was 0.0124 (95%CI: 0.007-0.021).
- For the third strata: The transmission rate β was 0.0162 (95%CI: 0.013-0.019) and the cure rate α was 0.0108 (95%CI: 0.0029-0.012).

The confidence intervals for the transmission coefficient (β) are overlapping between all the three strata, whereas the cure rate differs between strata 1 and 3. All parameters of the dynamic transmission model are listed in table 1. R_0 of strata 2 and 3 are > 1 indicating infectious properties of the bacteria whereas this is not the case for strata number 1. The difference in R_0 between the strata is reflected in differences in the proportion of cows entering and leaving the herd (μ) throughout the 12 months investigation period (table 1). Also the proportion of infected (θ_I) entering the lactation pen increased from strata 1 throughout strata 3.

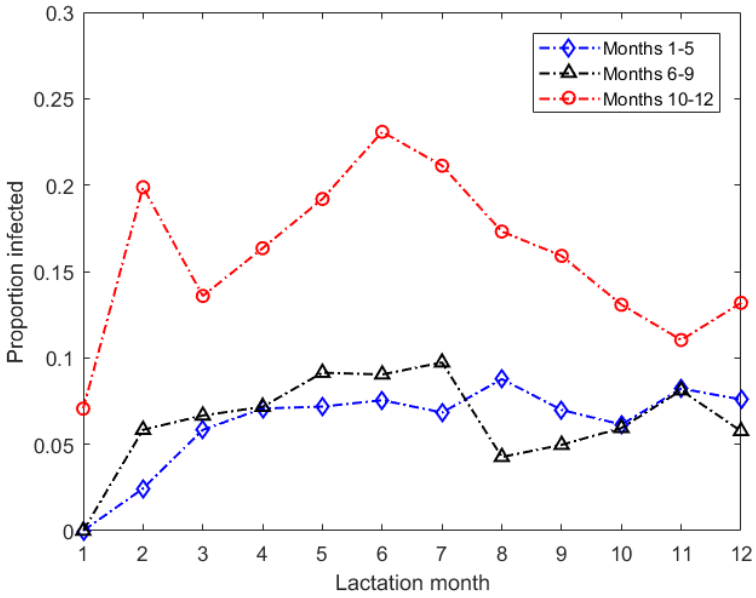

Figure 3. Transmission of *Corynebacterium* spp. with stratification: (1) Strata 1: from period 1 until period 5; (2) Strata 2: from period 6 until period 9; (3) Strata 3: from period 10 until period 12.

5. Discussion

The difference in R_0 of *Corynebacterium* spp. between strata 1 and the two later strata (2 and 3) of the calendar year coincides with changes in the daily rate of udders leaving and entering the lactation pen (μ) and is not related to differences in transmission coefficients or cure rates between the strata. The rate of cows leaving and entering the lactation pen is influenced by management related factors such calving season. This illustrates the importance of evaluating transmission of pathogen bacteria in a manner that takes seasonal variation in the composition of the population into account. In this case, infectious properties of the bacteria, that otherwise

Table 1. Estimation of the parameter of the SIS-model within strata 1, strata 2 and strata 3

Parameters	Strata 1	Strata 2	Strata 3
β	0.0187	0.0233	0.0162
α	0.0235	0.0124	0.0108
μ	0.01	0.0044	0.0037
θ_S	0.941	0.911	0.902
θ_I	0.059	0.089	0.098
$R_0 = \frac{\beta}{\mu+\alpha}$	0.5568	1.38	1.123

would have been hidden, became apparent during periods when the transfer of animals in and out of the compartment was low. Our knowledge on animal husbandry also tells us that this stationary phase coincides with the period of the year when most cows are lactating. In other words during a period of the year when most cows are in the mid-lactation period. Modelling of the transmission by lactation period show that this is the period of maximum transmission of *Corynebacterium* spp. i.e. the highest number of new infections.

Taken together, by using lactation month as the time variable within strata of calendar time, we can observe whether the nature of the infection (infectiousness), differs between consecutive strata. If there is a difference in modelling parameters between strata, this is a strong indicator for the influence of seasonal / managerial factors on our estimates of infectiousness of a disease. The approach of modelling by lactation moths also reveals the critical time periods of disease transfer relative to calving. For *Corynebacterium* spp. it became apparent that mid lactation was the most critical period of transfer of the bacteria, which, to our knowledge, has not been shown before. Figure 3 also shows that the pattern of a higher rate of new infections during mid lactation persists in all three 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 three 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 three strata new infections during mid lactation are detected but with different magnitude.

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