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Transmission dynamics of intramammary infections caused by *Corynebacterium* species

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ABSTRACT

The development of reliable models for transmission of intramammary infections (IMI) is the subject of extensive research. Such models are useful to enhance the identification and understanding of factors that affect pathogen-specific IMI dynamics. Longitudinal transmission models are valuable for predicting infection outbreak risks, quantifying the effectiveness of response tactics, and performing response planning. In this work, we focused on modeling *Corynebacterium* spp. by using a compartmental model. Previous investigations have considered modeling the transmission dynamics of several bacterial pathogens, but not *Corynebacterium* spp. We established a *Corynebacterium* spp. Susceptible–Infectious–Susceptible (SIS) model. We simulated the model numerically by using parameters that we estimated by a generalized linear model approach, using month of study as the time variable. The data, from which the parameters of the model were estimated, were obtained in a field trial conducted in 2 US dairy herds. Altogether, 786 cows were sampled at least once during the 13-mo study period. The total number of quarter milk cultures and cases of IMI caused by *Corynebacterium* spp. were 11,744 and 556, respectively, in farm A; the corresponding figures for farm B were 11,804 and 179. Our modeling study included only transmission from persistent IMI caused by *Corynebacterium* spp. within the lactation pens. The rate of new infections was significantly related to preexisting IMI in both farms, underscoring the importance of preexisting *Corynebacterium* spp. IMI for the transmission of *Corynebacterium* spp. within lactation pens. The estimated basic reproduction numbers (R_0) in the 2 farms were 1.18 and 0.98, respectively. The nonsignificant disparity in R_0 was associated with significant differences in cure rates between farms.

Key words: intramammary infection, *Corynebacterium* spp., transmission model

INTRODUCTION

Mastitis is one of the economically most important diseases in dairy production (Halasa et al., 2007; Hogeveen et al., 2011). Much of the economic loss is due to reduced milk production following subclinical mastitis (Hogan et al., 2016). Intramammary infections with *Corynebacterium* spp. are generally mild with limited milk production loss. However, significant elevations in SCC have been observed (Brooks et al., 1983; Brooks and Barnum, 1984a). Although *Corynebacterium* spp. are classified as minor pathogens (Brooks and Barnum, 1984b; Harmon, 1994; Blagitz et al., 2013), the increased prevalence of *Corynebacterium* spp. IMI in some modern dairy farms (Pitkälä et al., 2004) warrants further investigation into the specific properties and roles of the bacteria.

Some authors have reported a protective effect of *Corynebacterium* spp. IMI against IMI caused by other pathogens (Rainard and Poutrel, 1988; Lam et al., 1997a), whereas others report an increased risk of mastitis (Pankey et al., 1985; Berry and Hillerton, 2002; Parker et al., 2007). When investigating the relationship between secondary infections and a preexisting IMI by *Corynebacterium* spp., Parker et al. (2007) suggested that the diverging effects reported for *Corynebacterium* spp. IMI were due to the increased disposition for clinical mastitis of glands with a preexisting IMI. There is also evidence that *Corynebacterium bovis* can colonize the teat canal without affecting the udder past Furstenberg's rosette (Black et al., 1972).

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Mathematical models are powerful tools for understanding infection dynamics by providing predictions about the potential transmission of infections and the effectiveness of control measures (Magal and Ruan, 2008; Otto and Day, 2011). Pathogen-specific transmission patterns have been described for other major and minor mastitis pathogens (Lam, 1996; Zadoks et al., 2002; White et al., 2006; Reksen et al., 2012; Barlow et al., 2013), but not for *Corynebacterium* spp. The basic reproduction number, $\boldsymbol{R_0}$, is used in compartmental transmission models to determine 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 (Grossman, 1980; Diekmann et al., 1990; Hethcote, 2000). Modeling the progression of a disease depends on appropriate parameter values that are often unknown and must be estimated from field data. In this study, we have used a generalized 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 within lactation pens.

The main aim of this study was to develop a novel mathematical description of the transmission dynamics of *Corynebacterium* spp. IMI. Specifically, we first wanted to assess the importance of preexisting IMI by *Corynebacterium* spp. on new IMI caused by this group of bacteria. Second, we wanted to compare transmission parameters and cure rates for *Corynebacterium* spp. IMI between 2 US dairy farms with differing prevalences of *Corynebacterium* spp. IMI.

MATERIALS AND METHODS

Field Study

Data were obtained from a 13-mo longitudinal observational study in 2 commercial Holstein dairy herds (one in New York and one in Vermont). Cows were housed in pens of approximately 100 cows and milked 3 times per day. In farm A, the monthly mean number of lactating cows was 319, the mean milk production per cow per day was 32.7 kg, and the average cow composite SCC was 404,000 cells/mL. In farm B, the monthly mean number of lactating cows was 346, the mean milk production per cow per day was 35.0 kg, and the average cow composite SCC was 292,000 cells/mL. The herds participated in a DHIA program with monthly milk quality testing. Both farms had reliable identification of animals and used standardized mastitis control practices, including pre- and postmilking teat disinfection and blanket dry-cow therapy. Further details on the herds, microbial analyses, and sampling framework have been published previously (Reksen et al., 2012; Barlow et al., 2013).

Quarter milk samples were collected monthly from approximately 200 lactating cows on each farm. Additional samples were collected within 3 d after parturition and when animals were moved to or from the lactation compartment.

Trained field technicians collected the scheduled monthly samples. Selected farm personnel, who had received training for this, obtained the additional samples. All samples were collected according to recommended guidelines (Hogan et al., 1999). Samples collected monthly were kept on ice after collection and during transport to the laboratory, where they were frozen before microbiological analyses. 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 (Hogan et al., 1999). 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 IMI with *Corynebacterium* spp. when meeting at least one of the following criteria: (1) $\geq$1,000 cfu/mL of the pathogen were cultured from a single sample, (2) $\geq$500 cfu/mL of the pathogen were cultured from 2 out of 3 consecutive milk samples, (3) $\geq$100 cfu/mL of the pathogen were cultured from 3 consecutive milk samples, or (4) $\geq$100 cfu/mL of the pathogen were cultured from a clinical sample (Zadoks et al., 2002). A case was considered clinical when there was abnormal milk, with or without pain or swelling in the udder, or systemic signs such as anorexia, lethargy, or elevated rectal temperature (Harmon, 1994). Positive bacterial cultures that did not meet any of the above criteria were classified as representing a transient colonization with *Corynebacterium* spp.

Statistical Analysis

Statistical analysis was conducted using SAS software (version 9.1; SAS Institute, Inc., Cary, NC). Transmission parameters (β) and cure rates (α) were calculated using the generalized linear model approach (PROC GENMOD). Evidence of overdispersion was evaluated and models were subsequently adjusted using an overdispersion parameter estimated from the ratio of the Pearson Chi-squared estimate divided by the remaining degrees of freedom (Pscale option).

The transmission parameter (β) was estimated in a linear model with number of new *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 (study month), β^* is the intercept in the equation $\ln\left(I_M\right) = \beta^* + \ln\frac{SI}{N}$, and the transmission coefficient β is expressed as e^{β}. A log link, assumption of a negative binomial distribution, and offset $\ln\frac{SI}{N}$ (Zadoks et al., 2002) were used. Wald 95% confidence limits were used to compare transmission parameters between farms. To evaluate the effect of an existing *Corynebacterium* spp. IMI on transmission dynamics, we compared the fit of a model with the complete offset term included and a model without the term I/N included in the offset by comparing the 2×log-likelihood ratios.

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) (Zadoks et al., 2002) were used; I = quarter-days infected in each monthly interval (study 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}. Wald 95% confidence limits were used to compare cure rates between farms.

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. A confidence interval for R_0 was calculated using 1.96 × the standard error obtained from log-transformations of the monthly R_0 expressions.

Model Formulation

The transmission dynamics of *Corynebacterium* spp. were explored by developing a Susceptible–Infectious–Susceptible (**SIS**) model. The model describes a population of lactating udder quarters divided into 2 compartments: (1) S denotes susceptible quarters with no *Corynebacterium* spp. IMI, and (2) I denotes quarters affected with IMI caused by *Corynebacterium* spp., where the compartments represent the proportion of lactating quarters in each state. The dynamics of state transitions are illustrated in Figure 1, and the model is described mathematically by the following nonlinear ordinary differential equations (**ODE**):

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\beta SI + \alpha I + \theta_S N\mu - \mu S, \qquad [1]$$

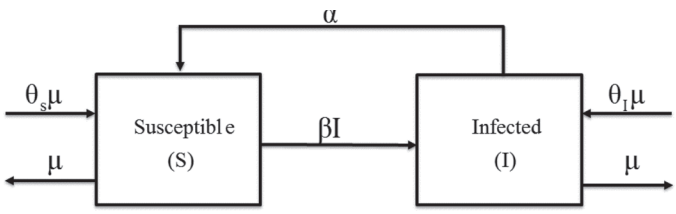

Figure 1. Schematic representation of the mathematical model of transmission of IMI with *Corynebacterium* spp. The boxes represent the state variables and the arrows represent the flow rates between susceptible (S) and infected (I) states. β = transmission parameter; βI = daily rate of new infections; α = daily rate of cured quarters; μ = daily rate of entry and exit of lactating quarters. The proportion of quarters into the S and I compartments are determined by θ_S and θ_I, respectively.

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta SI - \alpha I + \theta_I N\mu - \mu I, \qquad [2]$$

where 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 (Keeling and Rohani, 2011). The parameter α describes the daily rate of cured quarters, and 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.

The numerical resolution of the nonlinear ordinary equations of the SIS model was solved numerically by using a nonlinear programming solver of Matlab (MathWorks, Natick, MA), "ode45" solver, which is based on the Runge-Kutta method (Dormand and Prince, 1980). The numerical values of the parameters of the ODE of the SIS model, used in the numerical simulations, were obtained from the statistical analysis.

RESULTS

Field Study

In farm A, 11,744 milk samples were collected from a total of 371 cows. Among these, udder pathogens were cultured and identified in 5,021 samples. The distribution of bacterial culture results is given in Table 1. According to our definition of IMI, there were 556 *Corynebacterium* spp. IMI episodes during the study period, from 1,183 positive cultures; the remaining 1,618 positive samples were defined as transient colonizations. Of the 556 IMI episodes, 465 (84%) and 200 (36%) were associated with one or more samples having

Table 1. Distribution of microbiological diagnoses among samples positive for one or more udder pathogens

	Proportion (%)	
Culture result	Farm A	Farm B
Corynebacterium spp.	39.5	23.4
CNS	39.0	48.2
Streptococcus spp.	15.3	21.5
Staphylococcus aureus	2.7	0.9
Coliforms	1.4	4.8
Trueperella pyogenes	0.4	0.3
Streptococcus agalactiae	—	—
Other	1.7	0.9

≥1,000 or ≥5,000 cfu/mL, respectively. The distribution of quarter samples according to this categorization is shown in Table 2. Among IMI episodes, 3 cultures of *Corynebacterium* spp. were isolated in association with clinical cases. These were all co-infections with other minor pathogens and were not treated. Bacteriological milk culture was performed before and after the dry period in 471 quarter samples. Of these, 37 quarters were dried off while harboring a *Corynebacterium* spp. IMI. At the start of the next lactation, 36 of those were cured and 1 IMI persisted. Out of 434 quarters dried off without a *Corynebacterium* spp. IMI, 31 quarters were infected during the dry period.

In farm B, 11,804 milk samples were collected from a total of 415 cows. Among these, udder pathogens were cultured and identified in 3,528 samples. The distribution of bacterial culture results is given in Table 1. According to our definition of IMI, there were 179 *Corynebacterium* spp. IMI episodes during the study period from 255 positive cultures; the remaining 816 positive samples were defined as transient colonizations. Of the 179 IMI episodes, 147 (82%) and 15 (8%) were associated with one or more culture results with more than 1,000 and 5,000 cfu/mL, respectively. The distribution of quarter samples according to this categorization is shown in Table 2. Among IMI episodes, no cultures were isolated in association with clinical cases of *Corynebacterium* spp. IMI. Bacteriological milk culture was performed both before and after the dry period in 506 quarter samples. Of these, 13 quarters were dried off while harboring a *Corynebacterium* spp. IMI. At the start of the next lactation, all 13 quarters were cured. Out of 493 quarters dried off without *Corynebacterium* spp. IMI, 3 quarters were infected during the dry period.

Estimation of Transmission Parameters

From the statistical analyses, we obtained the following values for farm A. The transmission parameter, β, was 0.0188 (95% CI: 0.0159–0.0222), the cure rate, α, was 0.0122 (95% CI: 0.0098–0.0152), the daily rate of udders leaving and entering the lactation pen, μ, was 0.0039 (95% CI: 0.0027–0.0050), and R_0 was 1.1767 (95% CI: 0.9269–1.5760).

The difference in 2×log-likelihood between the model predicting number of new IMI with $\ln\frac{SI}{N}$ used as the offset term and the model with only $\ln S$ as the offset was 138.9. With 1 df, the Chi-squared statistic predicted a highly significant effect of an existing IMI with *Corynebacterium* spp. on the transmission of the bacteria from infected to susceptible quarters ($P < 0.001$).

The proportion of infected by days of study, as obtained from the raw data, is presented in Figure 2. This curve shows the evolution of the infection throughout the study period. The prevalence of infection began to increase after 215 d of study.

From the statistical analyses, we obtained the following values for farm B. The transmission parameter, β, was 0.0239 (95% CI: 0.0197–0.0291). The cure rate, α, was 0.0202 (95% CI: 0.0161–0.0253), the daily rate of udders leaving and entering the lactation pen, μ, was 0.0040 (95% CI: 0.0029–0.0051), and R_0 was 0.9879 (95% CI: 0.6632–1.4846). The 95% CI for α did not overlap between farms, whereas the corresponding CI for β, R_0, and μ were not different between farms.

The difference in 2×log-likelihood between the model predicting number of new infections with $\ln\frac{SI}{N}$ used as the offset term and the model with only $\ln S$ as the offset was 7.27. With 1 df, the Chi-squared statistic predicted a significant effect of an existing IMI with

Table 2. Number of samples with positive *Corynebacterium* spp. culture results

	Corynebacterium spp. positive		*Corynebacterium* spp. IMI	
Count (cfu/mL)	Farm A	Farm B	Farm A	Farm B
≥5,000	218	16	218	16
≥1,000 and <5,000	330	140	330	140
≥500 and <1,000	409	298	158	53
≥100 and <500	1,844	617	477	46

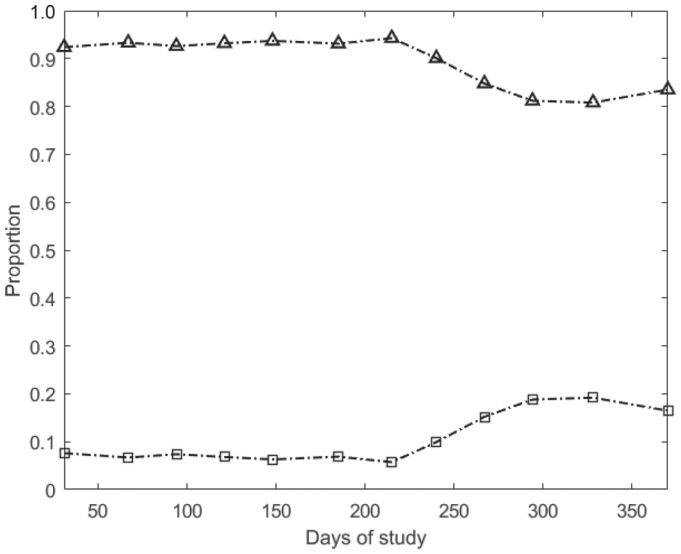

Figure 2. Proportion of quarters in farm A harboring an IMI (I; □) with *Corynebacterium* spp. and susceptible quarters (S; Δ) throughout the study period.

Corynebacterium spp. on the transmission of the bacteria from infected to susceptible quarters ($P < 0.01$).

The proportion of infected quarters by time, as obtained from the raw data, is presented in Figure 3. This curve shows the evolution of the infection throughout the study period. The prevalence of infection on farm B may be characterized as uniformly low throughout the study period.

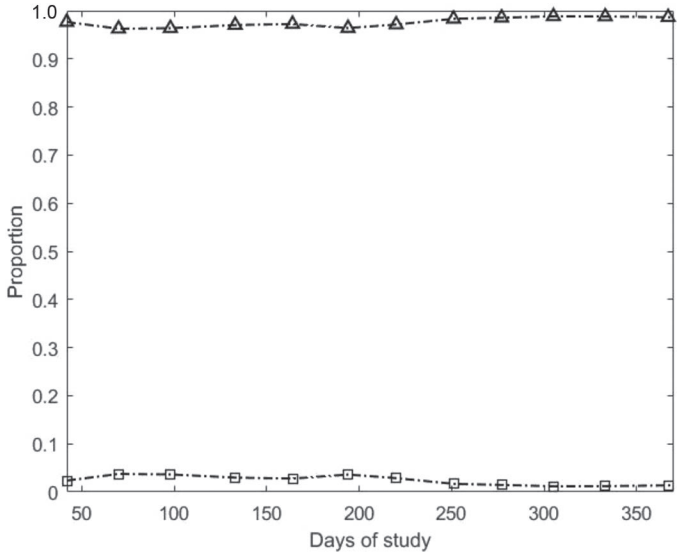

Figure 3. Proportion of quarters in farm B harboring an IMI (I; □) with *Corynebacterium* spp. and susceptible quarters (S; Δ) throughout the study period.

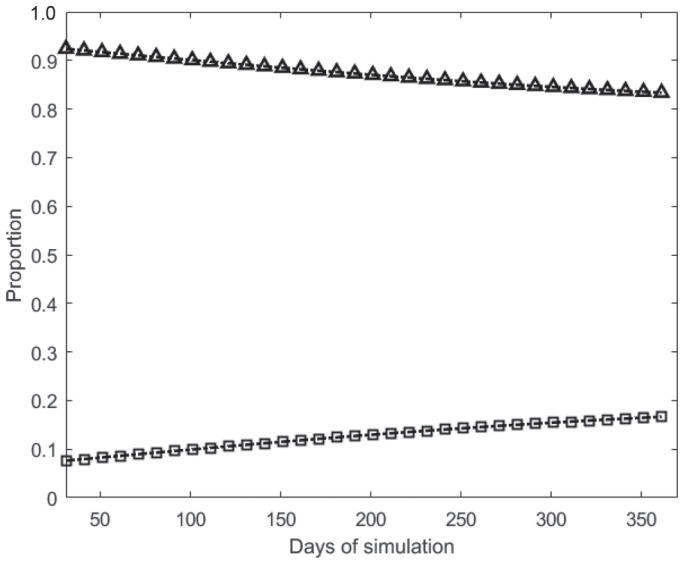

Figure 4. Simulation of the proportion of quarters in farm A harboring an IMI (I; □) with *Corynebacterium* spp. and susceptible quarters (S; Δ) using the Susceptible–Infectious–Susceptible (SIS) model. The values after initialization were $I_0 = 0.07613$ and $S_0 = 0.9239$.

Numerical Simulations

The proportions of I and S quarters from the dynamic simulation for farm A are presented in Figure 4. The proportion of I quarters increased throughout the simulation period, reaching a prevalence of 16.7% at 361 d on farm A. Figure 5 shows the proportion of I and S quarters on farm B. The proportion of I quarters was uniformly low throughout the simulation period on farm B.

DISCUSSION

By plotting the proportion of *Corynebacterium* spp. IMI by study days, we demonstrated an increase in the proportion of infected quarters from 215 d of study (December) and onward in farm A. We did not demonstrate a similar increase in the rate of new infections on farm B. For farm A, we obtained an R_0 of 1.18 that was not significantly different from the corresponding value for R_0 (0.98) on farm B. However, the number of IMI by *Corynebacterium* spp. developed differently between the 2 farms throughout the study period. Although the transmission of a pathogen is described by R_0 at the population level, it is the rate of both entry and exit of quarters, the transmission parameter, and the cure rate or duration of infection that determines the value of R_0. In our investigation, there was no significant difference between farms for the transmission parameters or the rates of entry and exit of quarters. However,

we found that cure rates were significantly different between farm A and farm B. The lower cure rate in farm A increased the R_0 for this herd, which explains the steady increase in new infections caused by preexisting IMI with *Corynebacterium* spp. in this farm. Correspondingly, the significance of a preexisting IMI with *Corynebacterium* spp. was demonstrated for both farms when we compared models with and without an existing IMI included in the offset term. The association between preexisting IMI and new infections was highly significant in farm A.

Biologically, it is plausible to relate the duration of infection to immunological characteristics of the host, or the animal's ability to eliminate an infection. It is worth noting that the cure rate during the dry period was high, with only 1 of 37 *Corynebacterium* spp. IMI persisting from one lactation to the next on farm A, and none out of 13 on farm B. However, we cannot quantify the degree of self-cure because blanket dry-cow therapy was used in the study herds.

Transmission of *Corynebacterium* spp. IMI depending on preexisting IMI has not, to our knowledge, been documented previously. There may be many reasons for the observed increase in new infections in our study, but it is worth noting that the increase started in December, which is the beginning of winter in New York and Vermont. Seasonal factors may thus have contributed to an increase in the infectious transmission of udder pathogens, including more wet and cold udders, damper environments, and so on. Because our diagnostics were limited to classifying at the *Corynebacterium* spp. level, we cannot exclude a shift toward more contagious subtypes, resulting in an alteration of transmission characteristics of the bacterial population in farm A. The deterministic state transmission simulation model shows how the epidemic evolves in a population of cows over time. This model will be suitable for modeling the long-term effect of the transmission parameters on the herd prevalence of *Corynebacterium* spp. IMI, and for modeling the effect of prophylactic interventions.

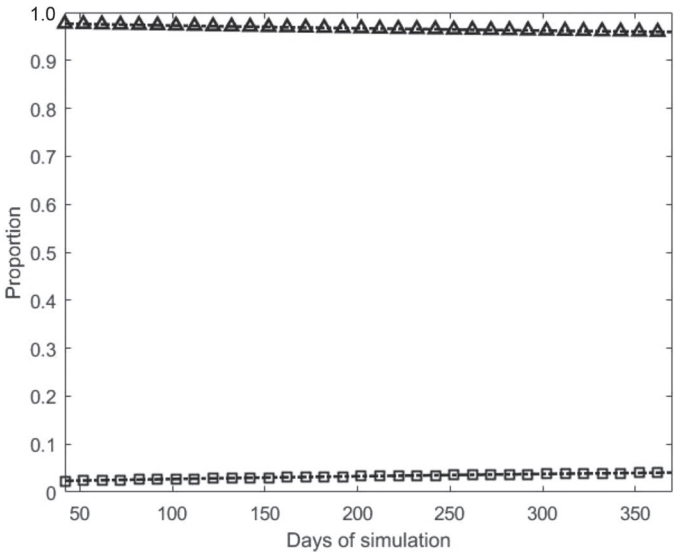

Figure 5. Simulation of the proportion of quarters in farm B harboring an IMI (I; □) with *Corynebacterium* spp. and susceptible quarters (S; Δ) using the Susceptible–Infectious–Susceptible (SIS) model. The values after initialization were $I_0 = 0.02346$ and $S_0 = 0.9765$.

Very few, if any, studies have attempted to quantify the infection dynamics of *Corynebacterium* spp. in dairy farms. However, observational studies have indicated that the prevalence of this minor pathogen is related to the quality of postmilking teat disinfection in dairy herds (Brooks et al., 1983; Harmon et al., 1986; Hogan et al., 1994; Lam et al., 1997b; Berry and Hillerton, 2002; Williamson and Lacy-Hulbert, 2013). In accordance with this, the present study showed that udder infections contribute significantly in the transmission of *Corynebacterium* spp. IMI. We observed 735 cases of IMI, 3 of which were from clinical cases. From the biological perspective, transient colonization does not necessarily equal IMI. Therefore, we limited our modeling to our definition of IMI.

It should be noted that the results we obtained were from 2 herds with different prevalences of *Corynebacterium* spp. IMI, despite being of similar size and having comparable management routines. We cultured *Corynebacterium* spp. from 23.9% of the quarter samples from farm A, but from only 9.1% of the quarter samples in farm B. The prevalence in farm A was relatively high compared with that reported in other publications (Brooks et al., 1983; Pitkälä et al., 2004; Green et al., 2005). In farm A, a higher proportion of the IMI episodes were associated with culture results having >5,000 cfu/mL than in farm B. This higher shedding level might contribute to an increased transmission potential on farm A. However, the estimated transmission parameter, β, did not differ between the 2 farms. Therefore, the observed difference in duration of infection and proportion of quarters shedding >5,000 cfu/mL might be attributable to host–pathogen factors associated with the ability of the cows to respond to, and clear, the infections. A study on *Salmonella* suggested that the prevalence of different infected states within or between herds could be due to a combined effect of host immunity, herd, and *Salmonella* serotype characteristics (Lanzas et al., 2008).

In the classic infectious disease epidemic SIR models (Anderson and May, 1991), the total population is divided into a susceptible compartment (S), an infected compartment (I), and a recovered compartment (R),

where recovered individuals are often considered to be resistant or removed from the susceptible population. In our modeling study, we adjusted the traditional SIR model with modifications specific to mastitis transmission in dairy herds, where cure and reinfection of individuals are observed, and it is assumed that recovery does not confer absolute resistance to reinfection. This could be described by an SIS model (Lam et al., 1996; White et al., 2001; Reksen et al., 2012), where the total number of quarters is divided into susceptible quarters (S) and infected quarters (I), assuming that susceptibility does not differ between naive individuals and recovered quarters.

CONCLUSIONS

The current study presents an investigation of transmission dynamics of *Corynebacterium* spp. IMI. The statistical analyses demonstrated that transmission of *Corynebacterium* spp. IMI in the 2 herds studied were influenced by preexisting *Corynebacterium* spp. IMI. In 1 of the 2 farms, the prevalence of *Corynebacterium* spp. IMI increased, consistent with an observed $R_0 > 1.0$ related to a low cure rate of *Corynebacterium* spp. IMI in this farm.

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