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The effect of *Mycobacterium avium* ssp. *paratuberculosis* infection on clinical mastitis occurrence in dairy cows

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ABSTRACT

Endemic diseases can be counted among the most serious sources of losses for livestock production. In dairy farms in particular, one of the most common diseases is Johne's disease, caused by *Mycobacterium avium* ssp. *paratuberculosis* (MAP). Infection with MAP causes direct costs because it affects milk production, but it has also been suspected to increase the risk of clinical mastitis (CM) among infected animals. This might contribute to further costs for farmers. We asked whether MAP infection represents a risk factor for CM and, in particular, whether CM occurrences were more common in MAP-infected animals. Our results, obtained by survival analysis, suggest that MAP-infected cows had an increased probability of experiencing CM during lactation. These results highlight the need to account for the interplay of infectious diseases and other health conditions in economic and epidemiological modeling. In this case, accounting for MAP-infected cows having an increased CM occurrence might have nonnegligible effects on the estimated benefit of MAP control.
Key words: Johne's disease, *Mycobacterium avium* ssp. *paratuberculosis*, clinical mastitis, dairy farm, comorbidity

INTRODUCTION

Endemic livestock diseases represent a serious economic burden for the livestock production economy. In the context of dairy farms, an analysis of diseases in Canadian dairy herds found that annual production losses and treatment costs for an average herd were $2,472 for Johne's disease (**JD**), $2,421 for bovine viral diarrhea, $2,304 for neosporosis, and $806 for bovine leukosis virus (Chi et al., 2002).

Johne's disease is a chronic degenerative disease of ruminants caused by intestinal infection with *Mycobacterium avium* ssp. *paratuberculosis* (**MAP**). In the US dairy industry MAP is currently endemic, with animal- and herd-level prevalences estimated to be around 4% and 35 to 68%, respectively (depending on whether 1 or 2 positive animals are necessary to consider the herd as positive; Garcia and Shalloo, 2015). However, due to the low sensitivity of current diagnostic tests, the true animal- and herd-level prevalences are likely to be higher (Lombard et al., 2013; Kirkeby et al., 2016). The estimated costs to the US dairy industry are more than $200 million/yr (Ott et al., 1999).

As no cure exists for MAP, control strategies are based on (1) the implementation of hygiene to reduce transmission and (2) surveillance through testing to promptly identify the infected animals and remove shedders (i.e., animals shedding MAP in their feces) from the herd (Pritchard et al., 2017). However, both these strategies might represent serious costs for the farm management. An individual farm's budget dedicated to animal health often is limited and must be divided between the management of multiple infectious diseases as well as other health conditions.

So far, many modeling approaches have been used to study the economics of disease control in dairy herds (Østergaard et al., 2000; Groenendaal et al., 2004; Cho et al., 2012; Archer et al., 2014), in particular for JD (Dorshorst et al., 2006; Cho et al., 2013; Smith et al., 2016). However, existing models meant to identify optimal strategies rarely tackle more than one issue at a time and thus miss the potential interdependent effect of JD and other clinical conditions.

The primary reason for the lack of models accounting for the interactions between JD and other diseases is a lack of information. The potential interactions between pathogens affecting cow health have not been precisely estimated. Among economically relevant health conditions, clinical mastitis (**CM**) is one of the most common problems in dairy farms. In fact, CM itself is estimated to cause on average about $90/case, including veteri-

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nary, treatment, and producer labor costs (Liang et al., 2017). Higher mastitis incidences (Diéguez et al., 2008) as well as a higher culling rate due to CM (Arrazuría et al., 2014) have been found in JD-positive farms, but the effect of MAP on individual animals' CM rates has not been determined.

The objective of this study was to understand whether MAP infection represents a significant risk factor for CM occurrence, particularly in animals with different MAP infection status. The results of this work can be further used in epidemiological modeling to obtain more accurate evaluation of the benefits of on-farm MAP control strategies.

MATERIALS AND METHODS

Data Collection and Description

In this study we used data provided by the Regional Dairy Quality Management Alliance (Ithaca, NY). All data were collected from 2 MAP-infected commercial dairy herds located in New York (farm A) and Pennsylvania (farm B), populated primarily with Holstein cows. A third farm in Vermont was included in the original dataset, but it was not considered in this study because no data on CM were recorded for this farm. Between 2004 and 2010, serum samples were collected quarterly and fecal samples were collected biannually from all adult animals on each farm. All monthly production and health records were obtained through the DHIA (Pradhan et al., 2009). Health records reported all noteworthy events regarding dairy production and were collected directly by herd managers; CM events, calving dates, pregnancies, abortions, and selling dates were included in these records. In this study, we considered only CM as registered in the health database. In particular, we reported the incidence of first CM by cow-year. When more than 1 CM case was recorded during the same lactation for the same cow, we disregarded all but the first CM for the sake of simplicity. The SCC data were reported on a monthly basis for each individual cow through the DHIA system, and this information was used to compare potential subclinical mastitis effects with CM results.

Milkers discovered most CM cases, characterized by a warm, swollen udder or changes in milk consistency. Cows with more severe disease symptoms were also detected by the herd manager. Mastitic cows were treated according to herd-specific practices that were consistent throughout the study but differed between herds. Communication with farm personnel during the data collection period suggested that milkers on farm A routinely recorded all cases of CM, whereas milkers on farm B mostly recorded severe cases of CM. Thus, CM definitions were not standardized between the 2 farms. To analyze the effect of this inconsistency, we considered the farm as a factor in most of our analysis. In a limited number of CM cases (<10%), samples were submitted for culture, but given the small number, we excluded culture results from the analysis.

All serum and fecal samples were shipped overnight to the University of Pennsylvania (New Bolton). When possible, additional samples (serum, feces, and intestinal epithelium and lymph nodes) were also shipped to the laboratory within 1 d of collection for animals sent to slaughter and animals that died on farm during the study period. Serum samples were tested with the ParaChek ELISA (Prionics USA Inc., La Vista, NE) and reported as positive or negative. Fecal and tissue samples were tested by 4-tube culture, and results were reported as negative (no growth), low shedding (<50 cfu/tube in all tubes), or high shedding (>50 cfu in at least 1 tube).

Following the analyses described in detail by Smith et al. (2016), the collected samples were used to identify MAP status for each animal. All individuals were classified according to 3 different categorizations: (1) MAP infection status: negative or positive; (2) MAP progression status: negative, nonprogressing, or progressing; and (3) MAP shedding status: negative, latent (i.e., infected but not shedding), low shedding, and high shedding. The first criterion simply divided the animals between those never testing positive for MAP and those with at least 1 positive test, whereas the second test accounted for MAP progression (Smith et al., 2016). As with other mycobacterial diseases, some animals test positive but never become high shedding and never show symptoms; these are labeled nonprogressing. The third criterion takes into account the animal's current shedding status. Latent animals were infected but not shedding (as determined by later positive diagnostic tests), whereas shedding individuals were divided into 2 categories: low shedding (ELISA positive only or low positive fecal culture) and high shedding (high positive fecal culture). Farm A records showed that high-shedding animals were removed after high positive fecal culture with a stated reason of JD, and both farms were shown to have increased culling rates in high-shedding animals (Smith et al., 2010). For that reason, high-shedding animals were excluded from the study, as the removal due to high-shedding status would violate the survival analysis assumptions of independent censoring.

As most infections are assumed to happen during calfhood and thus before the first lactation, we assumed that negative animals maintain their status throughout their life (Smith et al., 2016). For the same reason,

criteria 1 and 2 classifications were considered constant for each animal throughout the course of the study. However, the criterion 3 classification might change over time (e.g., an animal might be latent during an early lactation but change to low shedding in a following lactation). For this study, MAP shedding classification for a particular lactation was defined by the animal's status at the beginning of the lactation.

Survival Analysis

To define whether first CM was occurring significantly earlier in MAP-infected animals, we used a survival analysis approach. We calculated the time to mastitis for each cow–lactation combination, defined as the period length (d) from the beginning of the lactation (calving day) to the first CM event or the end of the lactation, whichever occurred first. Early abortions were ignored, whereas late abortion dates were substituted for calving dates when there was evidence of a following lactation. All animals that did not experience a case of CM during a lactation were considered as right-censored data, and the dry or cull date was set as the time of censoring. Other events that could result in a right-censored lactation included on-farm death and removal from the herd (sold or slaughtered). Records for which a credible end date was not available were set to be censored at 400 d, considering this threshold as the maximum lactation length. Lactations that started outside the farm were excluded from the study because it was not possible to define whether a CM event happened before purchase.

Survival curves were fitted through a Kaplan–Meier estimator and then compared using a log-rank test. The analysis was repeated for each of the 3 criteria listed (MAP infection, progression, and shedding status). A Cox proportional-hazard model was also fitted on the data to understand the potential effect of 2 covariates, farm (A or B) and parity.

An important objective of this study was to provide modelers an estimation of the CM occurrence risk parameters for a given MAP infection status. To obtain this, we fitted the CM survival curve using 5 distribution models: exponential, Weibull, log-normal, Gaussian, and logistic. The best fitting distribution was determined by log-likelihood test.

SCC Analysis

The effect of each MAP criterion on SCC was estimated using a mixed model approach with log-transformation of SCC. Covariates were included to account for herd, parity (as defined above), DIM, and season (winter: January to March; spring: April to June; summer: July to September; fall: October to December). Cows' unique ID was included as a random variable, with first-order autocorrelation by month in milk. An additional variable was added to criterion 3, indicating the months at a particular MAP status, as per Smith et al. (2016).

All analyses were done using R software (R Core Team, 2016) with the survival package (Therneau, 2015) for survival analysis and the nlme package (Pinheiro et al., 2017) for mixed model analysis. Figures were made using the package ggplot2 (Wickham, 2009).

RESULTS

Data Description

The study included 1,320 cows, of which 1,008 were in farm A and 312 were in farm B. Throughout this study we considered the lactating cow-year as the time unit for analysis. The number of cow-years was 2,688 in farm A and 624 in farm B for a total of 3,312 (Table 1).

There were 394 MAP-infected cow-years in farm A and 37 in farm B, whereas MAP infection was not defined for 139 cow-years (individuals not included in the sampling plan). Details on progression and shedding status are shown in Table 1. It was not possible to define the shedding status for 25 cow-years, all in farm A, because fecal culture data were not available. The incidence of total CM was 842 (802 in farm A and 40 in farm B). Among these, the incidence of first CM was 472 in farm A and 25 in farm B. Overall, in 317 cow lactations only 1 CM was registered; 101 cow lactations contained 2 CM events, and 79 cow lactations contained 3 or more CM events. The average incidence of first CM per lactation was 15.2% and ranged from 11.2% (sixth or higher lactation) to 19.8% (fourth lactation). Parities 6 and higher were combined for analysis because of the limited number of animals and cases (10 first CM in 89 cow-years). Overall, first CM incidence was 17.6% in farm A and 4.0% in farm B.

Survival Analysis Results

As shown in Figure 1A, MAP-positive animals had a higher risk of first CM, in particular for the first 150 d after calving. This was confirmed by the log-rank test (Table 2), in which the number of observed first CM in the MAP-positive individuals was about 40% higher than expected. Figure 1B shows the same curve, but here we divided the MAP-positive individuals in 2 further categories: progressing and nonprogressing (per criterion 2). As for the previous case, both non-

Table 1. The number of cows and lactations divided by commercial dairy farms A (New York) and B (Pennsylvania) and *Mycobacterium avium* ssp. *paratuberculosis* (MAP) infection status (criteria 1, 2, and 3; see Materials and Methods for details), including the number of lactations experiencing a first clinical mastitis (CM) event

Item (no. unless noted)	Farm A	Farm B	Total
Cows	1,008	312	1,320
Total cow-years	2,688	624	3,312
Mean years in lactation/cow (range)	2.66 (1–7)	2.00 (1–5)	2.46 (1–7)
First CM occurrences	472	25	497
First CM incidence (%)	17.6	4.0	15.2
MAP infection not defined	61	78	139
MAP negative	2,233	509	2,742
Criterion 1: MAP infection status			
MAP positive	394	37	431
Criterion 2: MAP progression			
Nonprogressing	306	35	341
Progressing	88	2	90
Criterion 3: MAP shedding status			
Latent (infected, test negative)	312	28	340
Low shedding	52	9	61
High shedding	5	0	5
Status not defined	25	0	25

progressing and progressing group curves demonstrated a higher risk for first CM, with 42 and 45% more first CM events than expected, respectively (Table 2). However, progressing animals were neither more nor less at risk for first CM than nonprogressing animals. When dividing the animals with respect to their shedding status (criterion 3), the analysis confirmed a higher risk of first CM for the latent group, which is clear in the Kaplan–Meier fitted curve (Figure 1C) and in the results of the log-rank test (Table 2), with about 47% more first CM events than expected. On the other hand, low-shedding individuals did not show a significantly different first CM occurrence risk from uninfected animals, as the Kaplan–Meier curve was very similar to that of the MAP-negative group and the number of observed first CM was about 4% lower than expected (9.4 vs. 9; Table 2). However, as highlighted in Figure 1C, the confidence interval of the low-shedding group curve was very wide, which might be attributable to the low number of cow-lactations in this group.

Table 3 shows the results of the Cox proportional-hazard regression model, which agrees with the Kaplan–Meier fitted curve: MAP-positive cows had a higher first CM risk than MAP-negative cows when considering criteria 1 and 2. With criterion 3, latent cows had a significantly higher risk for first CM (hazard ratio 2.09 compared with MAP-negative cows). Low-shedding cows had a nonsignificant decrease in first CM risk (hazard ratio = 0.88, 95% CI = 0.45–1.72, $P = 0.71$). This analysis also showed that parity was a risk factor (hazard ratio = 1.12) and that farm B had a lower first CM risk than farm A (hazard ratio = 0.25).

After fitting different distribution models on the first CM survival curve, we obtained the best results with the Weibull distribution (log-likelihood: −3,891) followed by log-normal (−3,903), exponential (−4,097), Gaussian (−4,410), and logistic (−4,449) models. Table 4 shows all Weibull distribution parameters for the different categories of each criterion. Similar to the Kaplan–Meier curve and the Cox proportional-hazard model, MAP-infected animals demonstrated a higher risk of first CM than their negative counterparts.

SCC Model Fit

In Figure 2 we reported the SCC distribution by farm (Figure 2A) as well as by cows' MAP infection status (Figure 2B). The results of the SCC analysis are shown in Table 5. Using criterion 1, MAP-positive animals had higher SCC values, but this result was not significant ($P = 0.097$). However, based on criterion 2, both progressing and nonprogressing animals had a significantly higher average SCC than MAP-negative animals ($P < 0.001$ for both), and progressing animals had a numerically higher average SCC than nonprogressing animals. Based on criterion 3, latent animals had higher average SCC than MAP-negative animals ($P < 0.001$) and a numerically higher average SCC than low-shedding animals. Low-shedding and high-shedding animals had a higher average SCC than MAP-negative animals; however, we could not rule out the basic null hypothesis of no difference in SCC values between these and the MAP-negative animals ($P = 0.10$ and 0.16, respectively). The number of months an animal had spent at a particular MAP status was not significantly related to SCC ($P = 0.055$) and thus was removed from the final model.

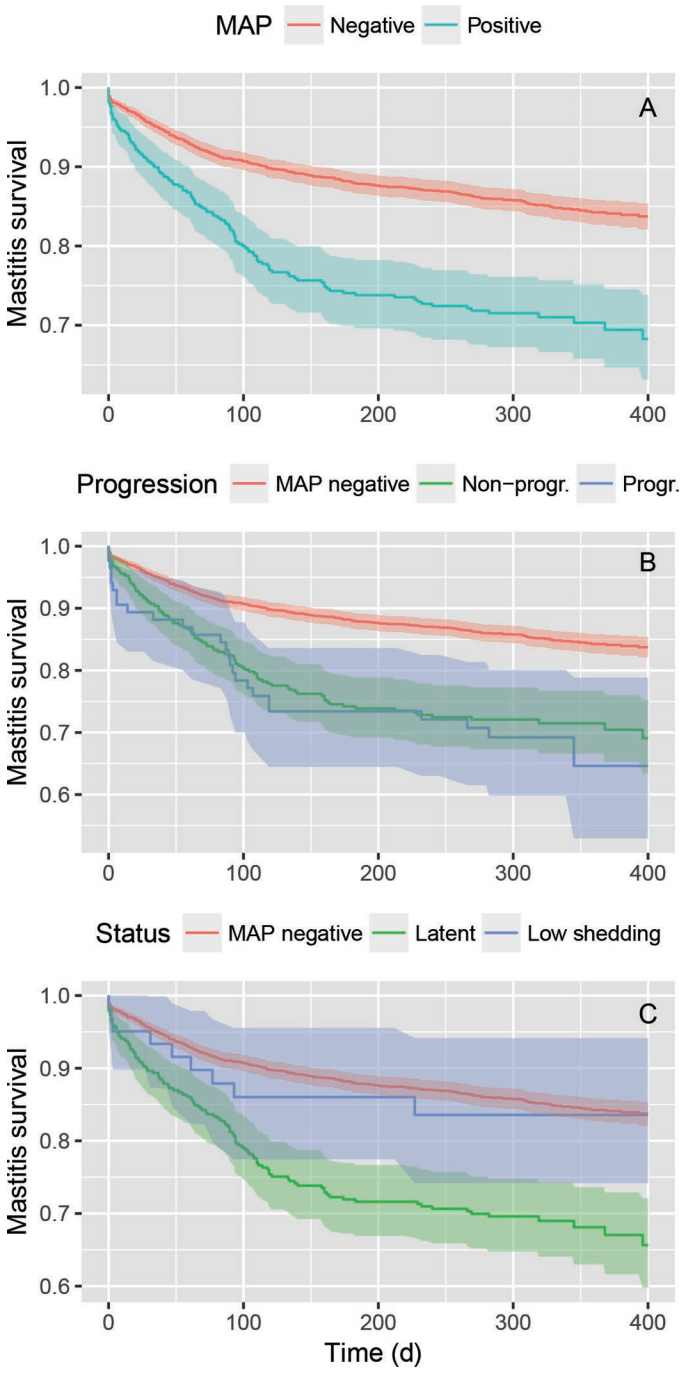

Figure 1. Results for the log Kaplan–Meier fitting curve on first clinical mastitis survival (the probability of no clinical mastitis) in commercial US dairy cows by lactation. Individuals were divided by the following criteria: (A) *Mycobacterium avium* ssp. *paratuberculosis* (MAP) positive and negative (criterion 1); (B) MAP negative, nonprogressing, and progressing (progr.; criterion 2); and (C) MAP negative, latent, and low shedding (criterion 3). Shaded areas represent the 95% confidence interval, and solid lines are the means. Color version available online.

DISCUSSION

The main objective of this analysis was to understand whether MAP infection is associated with a higher risk for CM. Our results, obtained by applying survival analysis to data from 2 dairy cattle farms in the northeastern United States (Pennsylvania and New York), suggest that MAP-positive animals might have a significantly higher risk of experiencing first CM compared with MAP-negative cows in the same herds.

On one hand, these results were anticipated, as it would be expected that infection with MAP might cause a weakened immune system, and therefore cows could be more susceptible to other infections (Pritchard et al., 2017). Moreover, results pointing in that direction have been found since the 1970s. In particular, at the farm level, JD has been significantly associated with higher rates of culling due to CM (Hasonova and Pavlik, 2006, and references therein). Unlike earlier studies, however, we have provided a solid estimate of differences in the risk of first CM occurrence for individual MAP-infected and noninfected animals, including all subcategories in which MAP positivity could be divided with respect to disease progression or shedding status.

Interestingly, we found that the increase in first CM risk associated with MAP infection was primarily observed in the latent individuals. In agreement with our results, Wilson et al. (1995) found that first CM was associated with subclinical but not clinical JD. It is possible that the immune system is negatively affected by MAP infection, leading to increased susceptibility to first CM. Our analyses also showed no significant differences between SCC values for MAP-negative and MAP-positive animals (criterion 1) and between MAP-negative and low- or high-shedding animals (criterion 3). This suggests that the power of our analyses might not be enough to confirm the observed trend, as the data were not originally collected for this purpose. In fact, the low number of individuals of low- and high-shedding status might have been a limiting factor for a correct evaluation of this phenomenon. Thus, more studies are needed to determine the underlying mechanism behind this.

The farms included in this study had a different CM and first CM reporting rate, with farm B reporting only severe CM cases. As a consequence, the farm covariate was a significant predictor for first CM occurrence according to the Cox proportional-hazard model fit. However, the results on the SCC analysis showed that farm was not a significant factor. Despite the different reporting rate, our main results hold for both farms.

In conclusion, our results highlighted how MAP-infected dairy cows have a higher incidence of CM than

Table 2. Results for the log-rank test on Kaplan–Meier estimation survival fit for first clinical mastitis (CM) occurrence in cow-years divided by the following criteria: (1) *Mycobacterium avium* ssp. *paratuberculosis* (MAP) infection status: positive and negative; (2) MAP progression status: negative, nonprogressing, and progressing; and (3) MAP shedding status: negative, latent (infected but not shedding), and low shedding (high shedding was excluded; see Materials and Methods)

Item	Total records (no.)	Observed first CM (no.)	Expected first CM (no.)	χ^2 (df)
Criterion 1				43.9 (1)*
MAP negative	2,742	370	420.4	
MAP positive	426	118	67.6	
Criterion 2				44.0 (2)*
MAP negative	2,742	370	420.4	
Nonprogressing	341	92	53.3	
Progressing	85	26	14.2	
Criterion 3				50.2 (2)*
MAP negative	2,742	370	418.9	
Latent (infected, test negative)	340	104	54.7	
Low shedding	61	9	9.4	

*$P < 0.001$ compared with MAP negative.

Table 3. The results for the Cox proportional-hazard regression model for clinical mastitis occurrence in cow-years divided by the following criteria: (1) *Mycobacterium avium* ssp. *paratuberculosis* (MAP) infection status: positive and negative; (2) MAP progression status: negative, nonprogressing, and progressing; and (3) MAP shedding status: negative, latent (infected but not shedding), and low shedding (high shedding was excluded; see Materials and Methods)[1]

Predictor	Hazard ratio	95% CI	*P*-value
Criterion 1			
MAP positive (vs. negative)	1.89	1.53–2.33	<0.001
Farm B (vs. A)	0.25	0.16–0.38	<0.001
Parity	1.12	1.05–1.19	<0.001
Criterion 2			
Nonprogressing (vs. MAP negative)	1.86	1.48–2.35	<0.001
Progressing (vs. MAP negative)	2.00	1.34–2.98	<0.001
Farm B (vs. A)	0.25	0.16–0.38	<0.001
Parity	1.12	1.05–1.19	<0.001
Criterion 3			
Latent (infected, test negative) status (vs. MAP negative)	2.09	1.68–2.60	<0.001
Low shedding status (vs. MAP negative)	0.88	0.45–1.72	0.71
Farm B (vs. A)	0.25	0.16–0.38	<0.001
Parity	1.12	1.07–1.21	<0.001

[1]The other predictors included in the model are farm (A or B) and individual parity (1–10).

Table 4. Weibull distribution parameters for the first clinical mastitis occurrence survival curve, calculated for different *Mycobacterium avium* ssp. *paratuberculosis* (MAP) infection criteria: (1) MAP infection status: positive and negative; (2) MAP progression status: negative, nonprogressing, and progressing; and (3) MAP shedding status: negative, latent (infected but not shedding), and low shedding (high shedding was excluded; see Materials and Methods)

Parameter	Value	SE	95% CI	*P*-value
Criterion 1				
Shape: MAP negative	9.66	0.21	9.26 to 10.07	<0.001
Shape: MAP positive	−1.64	0.24	−2.10 to −1.18	<0.001
Log(scale)	0.76	0.04	NA[1]	<0.001
Criterion 2				
Shape: MAP negative	9.66	0.21	9.26 to 10.07	<0.001
Shape: nonprogressing	−1.59	0.26	−2.09 to −1.08	<0.001
Shape: progressing	−1.86	0.44	−2.72 to −1.00	<0.001
Log(scale)	0.76	0.04	NA	<0.001
Criterion 3				
Shape: MAP negative	9.66	0.21	9.26 to 10.07	<0.001
Shape: latent (infected, test negative)	−1.59	0.26	−2.09 to −1.08	<0.001
Shape: low shedding	−1.86	0.44	−2.72 to −1.00	<0.001
Log(scale)	0.76	0.04	NA	<0.001

[1]NA = not available.

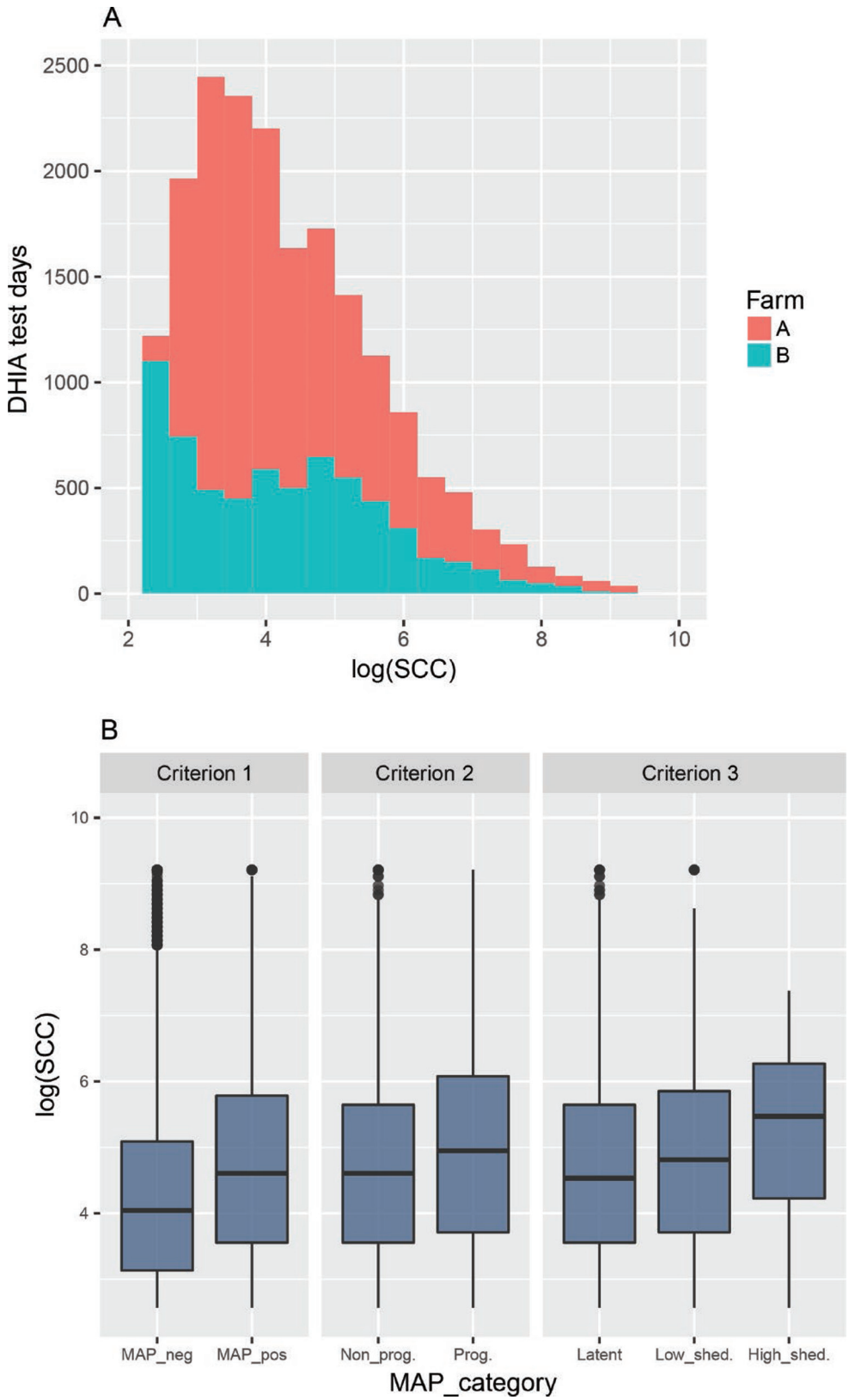

Figure 2. Somatic cell count data. (A) Distribution of (log) SCC values, divided by farm. (B) Distributions of (log) SCC values divided by MAP infection status: MAP negative (neg; for all 3 criteria); MAP positive (pos; criterion 1); nonprogressing and progressing (prog.; criterion 2); and latent, low shedding, and high shedding (shed.; criterion 3). Color version available online.

Table 5. The results of a mixed linear model for the effect of paratuberculosis status on the log of SCC in monthly DHIA test data divided by the following criteria: (1) *Mycobacterium avium* ssp. *paratuberculosis* (MAP) infection status: positive and negative; (2) MAP progression status: negative, nonprogressing, and progressing; and (3) MAP shedding status: negative, latent (infected but not shedding), and low shedding (high shedding was excluded; see Materials and Methods)[1]

	Criterion 1		Criterion 2		Criterion 3	
Predictor	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value
Intercept	3.539 (3.466, 3.612)	<0.001	3.502 (3.428, 3.576)	<0.001	3.52 (3.446, 3.593)	<0.001
DIM	0.002 (0.002, 0.002)	<0.001	0.002 (0.002, 0.002)	<0.001	0.002 (0.002, 0.002)	<0.001
Parity	0.221 (0.199, 0.242)	<0.001	0.217 (0.195, 0.238)	<0.001	0.214 (0.192, 0.236)	<0.001
Season: spring	−0.137 (−0.186, −0.088)	<0.001	−0.136 (−0.185, −0.087)	<0.001	−0.137 (−0.186, −0.088)	<0.001
Season: summer	−0.05 (−0.094, −0.006)	0.026	−0.053 (−0.098, −0.009)	0.018	−0.049 (−0.093, −0.005)	0.028
Season: winter	−0.076 (−0.121, −0.031)	0.001	−0.081 (−0.125, −0.036)	<0.001	−0.077 (−0.122, −0.032)	0.001
Farm B (vs. A)	−0.033 (−0.106, 0.039)	0.366	−0.016 (−0.089, 0.057)	0.662	−0.016 (−0.088, 0.056)	0.667
MAP positive	0.123 (−0.022, 0.268)	0.097				
Nonprogressing			0.285 (0.189, 0.382)	<0.001		
Progressing			0.519 (0.321, 0.717)	<0.001		
Latent status					0.287 (0.144, 0.43)	<0.001
Low shedding status					0.139 (−0.027, 0.304)	0.101
High shedding status					0.348 (−0.142, 0.838)	0.164

[1]The other predictors included in the model are farm (A or B) and individual parity (1–10).

MAP-negative cows. The added value of this analysis, as well as one of the motivating factors, was to provide a sound estimate of the CM risk parameters for different stages of MAP-infected animals. By using 3 different observable criteria for MAP infection categorization, our results can be applied to economic analyses using different assumptions about MAP biology. By including the combined effect of JD and CM in economic and epidemiological dynamic models, we could provide a more accurate estimate of the real burdens caused by some of the most common health issues in dairy farms.

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