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Tolerance to bovine clinical mastitis: Total, direct, and indirect milk losses

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ABSTRACT

The objectives of this paper were to estimate direct and indirect milk losses associated with mastitis. Indirect losses, linked to indirect tolerance, are mediated by the increase in milk somatic cell count (SCC) in response to bacterial infection. Direct losses, linked to weak direct tolerance, are not mediated by the increase in SCC. So far, studies have evaluated milk loss associated with clinical mastitis without considering both components, which may lead to biased estimates of their sum; that is, the total loss in milk. A total of 43,903 test-day records on milk and SCC from 3,716 cows and 5,858 lactations were analyzed with mediation mixed models and health trajectories to estimate the amount of direct, indirect, and total milk losses after adjustment for known and potentially unmeasured (sensitivity analyses) confounding factors. Estimates were formalized under the counterfactual causal theory of causation. In this study, milk losses were mostly mediated by an increase in SCC. They were highest in the first month of lactation, when SCC were highest. Milk losses were estimated at 0.5, 0.8, and 1.1 kg/d in first, second, and third and greater parity, respectively. Two phases described how changes in milk were associated with changes in SCC: on average, one occurred before and one after the day preceding the clinical diagnosis. In both phases, changes in milk were estimated at 1 mg/d per 10^3 cells/mL. After adjusting for known confounders, cow effect accounted for 20.7 and 64.2% of the variation in milk in the first and second phases, respectively. This suggests that deviations from the resilient path were highest during the second phase of inflammation and that selection for cows more tolerant to mastitis is feasible. As discussed herein, epigenetic regulation of macrophage polarization may contribute to the variation in milk observed in the second phase.

Key words: mastitis, health trajectory, mediation, tolerance, counterfactual

INTRODUCTION

Milk production decreases in cows with mastitis and the amount of milk lost is influenced by several factors including the level of "tolerance" of infected cows. Tolerance (e.g., Råberg et al., 2007) is the ability to reduce the negative consequences of infection by reducing the damage caused by pathogens (direct tolerance) or by the host response triggered by the infection (indirect tolerance). The distinction is important because only mechanisms of indirect tolerance are linked to those of resistance. The spread of an infectious disease will be limited without loss in performance if cows are resistant and indirectly tolerant. The distinction is also important because of the restrictions on therapeutics of mastitis. Usually, these include antimicrobials to kill bacteria (to be used to treat cows not directly tolerant) and anti-inflammatory drugs to reduce damage due to immune response (to be used to treat cows indirectly not tolerant).

In bovine mastitis, indirect tolerance mechanisms oppose effects of immune cells, including neutrophils that migrate from the blood into the infected gland. Routinely, this migration is evaluated by milk SCC. Then, milk loss mediated by the increase in SCC can be considered as a consequence of limited indirect tolerance (called "indirect loss" hereafter). Conversely, milk loss not mediated by the increase in SCC can be regarded as a consequence of limited direct tolerance (called "direct loss"). The sum of both represents the "total loss."

With a few exceptions (Detilleux et al., 2015), it is difficult to find separate estimates of milk losses in the literature. For example, Hagnestam-Nielsen et al. (2009) estimated losses by comparing test-day milk yields (**TDM**) of cows with and without mastitis after adjusting for confounding factors known to affect milk production but without considering concomitant changes in SCC. These are estimates of the total loss. In other studies, researchers estimated milk losses by

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regressing measures of SCC on TDM, also adjusting for various control variables (e.g., Koldeweij et al., 1999; Dürr et al., 2008) but without knowing the mastitis status of the cows. These are estimates of the indirect loss.

Mediation analyses can be used to obtain separate estimates of milk losses. In these analyses, a mediating variable (e.g., SCC) conveys the influence of an independent variable (e.g., presence vs. absence of clinical mastitis) on a dependent variable (e.g., TDM). Then, under the counterfactual framework (e.g., Vanderweele and Vansteelandt, 2009; Richiardi et al., 2013), the direct effect would be measured by the expected difference in TDM in the presence versus absence of mastitis when SCC remain unchanged. The indirect effect is measured by the expected difference in TDM when SCC are measured in the presence and absence of mastitis.

It has also been argued that estimates of tolerance may be different according to the stage of infection and that health trajectories may capture this dynamic (Schneider, 2011; Lough et al., 2015). Health trajectories are curves that link the values of indicators of health and infection at many time points over the course of the disease. This produces looping curves that can be partitioned in different sections reflecting different infection stages. They are also useful to determine whether diseased individuals recover and if the infection is cleared (resilient system).

The goals of this study were (1) to apply a mediation model on and construct heath trajectories of TDM collected during a field study on cows with and without clinical mastitis; (2) to obtain estimates of associated total, direct, and indirect milk losses; and (3) to interpret these estimates under the counterfactual framework.

MATERIALS AND METHODS

Data Description

Data came from a 3-yr survey of 30 commercial dairy farms conducted by the group "Observatory for Udder Health (OSaM)" that connects researchers, dairy associations, and breeders in collecting information on farm, animal, and clinical mastitis events in the Walloon region of Belgium (Reding et al., 2011). Herds were enrolled in the regional dairy herd recording system from which monthly TDM (L/d) and SCC ($\times 10^3$ cells/mL) data were obtained. Edited data included TDM and SCC collected within the first 10 mo of lactation from cows in parity 1 to 3. When information was missing, it was imputed by linear interpolation between closest values. Other information included year of calving, parity, DIM, and number of days between successive events.

Clinical mastitis was diagnosed by the breeder when milk from one or more glands was abnormal in color, viscosity, or consistency, with or without accompanying signs of heat, pain, or redness. Two indicators of clinical mastitis (**CM**) were created: (1) if TDM and SCC were sampled on the day of diagnosis, then the first indicator (CM1) was set to 1, and at 0 otherwise; (2) if TDM and SCC were sampled 15 d before until 70 d after the day of diagnosis, then the second indicator (CM2) was set to 1, and at 0 otherwise. For records with CM2 = 1, individual trajectories were constructed by plotting individual measurements of TDM against SCC in 2-dimensional space at different times with respect to the day of diagnosis. The range was chosen in reference to the study by Gröhn et al. (2004), who observed a decline in milk yield in the period from 15 d before until 70 d after diagnosis of mastitis.

Estimation of Milk Losses

Mediation Models. Two multiple regression equations (model [1]) were used to estimate the effects of clinical mastitis on TDM: one to estimate the effect of CM1 (or CM2) on SCC and the other to estimate the effects of CM1 (or CM2) and SCC on TDM:

$$\mathrm{E}(\mathrm{Y}^{\mathrm{i,t}}) = \nu + \beta_1\,\mathrm{A}^{\mathrm{i,t}} + \beta_2\,\mathrm{M}^{\mathrm{i,t}} + \beta_3\,\mathrm{C}^{\mathrm{i,t}} + \beta_4\,\mathrm{AM}^{\mathrm{i,t}} + \beta_5\,\mathrm{CM}^{\mathrm{i,t}} + \beta_6\,\mathrm{AC}^{\mathrm{i,t}} + \beta_7\,\mathrm{AMC}^{\mathrm{i,t}}$$

$$\mathrm{E}(\mathrm{M}^{\mathrm{i,t}}) = \exp(\mu + \delta_1\,\mathrm{A}^{\mathrm{i,t}} + \delta_3\,\mathrm{C}^{\mathrm{i,t}} + \delta_6\,\mathrm{AC}^{\mathrm{i,t}}),$$

where $\mathrm{Y}^{\mathrm{i,t}}$ ($\mathrm{M}^{\mathrm{i,t}}$) is the TDM (SCC) record of the ith cow at the tth day in lactation (t = 1, 2, ...300), ν and μ are the overall means; $\mathrm{A}^{\mathrm{i,t}}$ is the indicator variable for mastitis (either CM1 or CM2); $\mathrm{C}^{\mathrm{i,t}}$ represents the indicator variables for the known confounders in the association between TDM, SCC, and mastitis; β_j (δ_k) is the regression coefficient of $\mathrm{Y}^{\mathrm{i,t}}$ ($\mathrm{M}^{\mathrm{i,t}}$) on an explanatory variable for j = 1, 2, ..., 7 and k = 1, 3, 6. For example, the regression coefficient β_1 represents the change in TDM due to the presence of mastitis, keeping all other variables in the model held constant. The confounders are herd-year-season (1, 2, ..., 372), parity (1, 2, 3), and month in lactation (1, 2, ..., 10). Cow effect and residual were considered random and distributed normally and independently with null mean and variances that account for the repeated nature of the data (compound symmetry). The Genmod and Mixed procedures of SAS (version 9.3; SAS Institute Inc., Cary, NC) were