Preventive Veterinary Medicine 147 (2017) 124–131

Contents lists available at ScienceDirect

Preventive Veterinary Medicine

journal homepage: www.elsevier.com/locate/prevetmed

Marginal structural Cox model to estimate the causal effect of clinical mastitis on Québec dairy cow culling risk

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ARTICLE INFO

Keywords:
Culling
Dairy cow
Bias
Confounding
Time-varying
Marginalstructural model
Causal inference
Survival

ABSTRACT

Health disorders, such as milk fever, displaced abomasum, or retained placenta, as well as poor reproductive performance, are known risk factors for culling in dairy cows. Clinical mastitis (CM) is one of the most influential culling risk factors. However the culling decision could be based either on the disease status or on the current milk yield, milk production being a significant confounder when modelling dairy cow culling risk. But milk yield (and somatic cell count) are time-varying confounders, which are also affected by prior CM and therefore lie on the causal pathway between the exposure of interest, CM, and the outcome, culling. Including these time-varying confounders could result in biased estimates. A marginal structural model (MSM) is a statistical technique allowing estimation of the causal effect of a time-varying exposure in the presence of time-varying covariates without conditioning on these covariates. The objective of this paper is to estimate the causal effect on culling of CM occurring between calving and 120 days in milk, using MSM to control for such time-varying confounders affected by previous exposure. A retrospective longitudinal study was conducted on data from dairy herds in the Province of Québec, Canada, by extracting health information events from the dairy herd health management software used by most Québec dairy producers and their veterinarians. The data were extracted for all lactations starting between January 1st and December 31st, 2010. A total of 3952 heifers and 8724 cows from 261 herds met the inclusion criteria and were used in the analysis.

The estimated CM causal hazard ratios were 1.96 [1.57–2.44] and 1.47 [1.28–1.69] for heifers and cows, respectively, and as long as causal assumptions hold. Our findings confirm that CM was a risk factor for culling, but with a reduced effect compared to previous studies, which did not properly control for the presence of time-dependent confounders such as milk yield and somatic cell count. Cows experienced a lower risk for CM, with milk production having more influence on culling risk in cows than heifers.

1. Introduction

Health disorders, such as milk fever, displaced abomasum, or retained placenta (Rajala-Schultz and Gröhn, 1999a,b,c; Beaudeau et al., 2000), as well as poor reproductive performance (Schneider et al., 2007; De Vries et al., 2010), are known risk factors for culling in dairy cows. Among these risk factors, one of the most influential is clinical mastitis (CM; Gröhn et al., 1998; Rajala-Schultz and Gröhn, 1999a,b,c; Schneider et al., 2007); with the risk between mastitis and culling being time-dependent (Gröhn et al., 1997, 1998).

However, the culling decision could be based either on the disease status of the cow or on its current milk yield, milk production being a significant confounder when modelling dairy cow culling risk. High producing cows are at greater risk of mastitis (Schukken et al., 1991; Waage et al., 1998; Barnouin et al., 2005; O'Reilly et al., 2006), and a lower milk production compared to herd mates has a significant effect on culling decisions (Beaudeau et al., 1994; Rajala-Schultz and Gröhn, 1999a,b,c; Hadley et al., 2006). Moreover, cows that had an episode of CM are at greater risk for occurrence of other CM episodes later during their lactation (Lam et al., 1997; Zadoks et al., 2001). Similarly, a high somatic cell count (SCC) is a risk factor for mastitis as well as for culling (Caraviello et al., 2005; Sewalem et al., 2006; Steeneveld et al., 2008). The correct estimation of the effect of mastitis on culling requires the inclusion of milk yield (and SCC) in the modelling strategy. However,

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http://dx.doi.org/10.1016/j.prevetmed.2017.08.017
Received 23 December 2016; Received in revised form 18 August 2017; Accepted 19 August 2017
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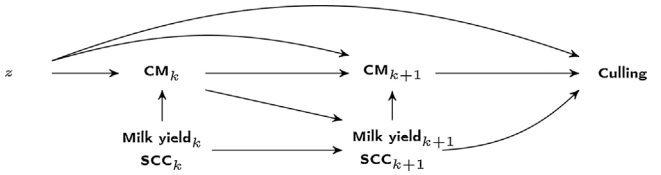

Fig. 1. Directed acyclic graph (DAG) for the effect of clinical mastitis on culling, with time points *k*. *z* is a vector of baseline covariates. CM, clinical mastitis; SCC, somatic cell count.

milk yield and SCC are time-dependent (or time-varying) confounders, which are also affected by prior CM (Rajala-Schultz et al., 1999; Seegers et al., 2003), i.e. intermediate covariates. Therefore these covariates lie on the causal pathway between the exposure of interest, CM, and the outcome, while at the same time being risk factors for culling, as depicted in the directed acyclic graph (DAG) in Fig. 1. Adjusting for variables that are confounders but also affected by prior exposure gives biased estimates of the true or 'causal' total effect. Failing to adjust for milk production and SCC would result in a biased effect estimate, yet adjustment for those variables would also result in biased estimates (Hernán et al., 2004; Cole et al., 2010). This methodological problem has been well described by Robins et al. (2000), Hernán et al. (2004), and Cole and Hernan (2008).

Marginal structural Cox models (MSM) provide the marginal causal relation between a time-varying exposure and a survival outcome (e.g. time to culling), controlling for time-varying confounders without conditioning on those variables (Robins et al., 2000; Hernán et al., 2000; Cole and Hernan, 2008). The regression model relates the exposure history up to time *t* to the counterfactual outcome at time *t*. Propensity scores that estimate the probability of a given level factor (e.g. CM) given measured confounders, are used within a MSM to weight subjects in order to create balanced groups of cows based upon the confounders used in the construction of the scores. An introduction to MSM methodology was described in Martin (2014). The weighting allows the construction, for a risk set at time *t*, of a 'pseudo-population' in which the time-varying confounders no longer predict CM at *t*, i.e. are no longer confounders, and the causal association between CM and culling is the same as in the original population (Hernán et al., 2000). Therefore the estimation of the unconfounded association between the exposure and outcome is now allowed without conditioning on the covariate in the regression model (Robins et al., 2000).

The issue of the direct and indirect effects of milk yield on culling risk due to mastitis was already raised by hn et al. (1997, 1998); hn et al. (1997, 1998). But biases due to time-varying confounders were not identified at that time and have not yet been properly addressed. The objective of this paper is to estimate the causal effect on culling of the time-dependent exposure CM, occurring between calving and 120 days in milk (DIM), by using a marginal structural model (Robins, 1999; Robins et al., 2000) to control for such time-varying confounders affected by previous exposure.

2. Materials and methods

2.1. Dataset

A retrospective longitudinal study was conducted on data from dairy herds in the Province of Québec, Canada, by extracting health information events from *DSA Laitier* (DSAHR Inc., Saint-Hyacinthe, QC, Canada), the dairy herd health management software used by more than half of Québec's producers and their veterinarians. This program uses clearly defined health definitions, ensuring that producers and veterinarians record the same health conditions, using the same definitions. Veterinarian enters health conditions into the herd DSA database, as well as producers for which data are then reviewed by their veterinarian at the herd visit. All information is transferred into the

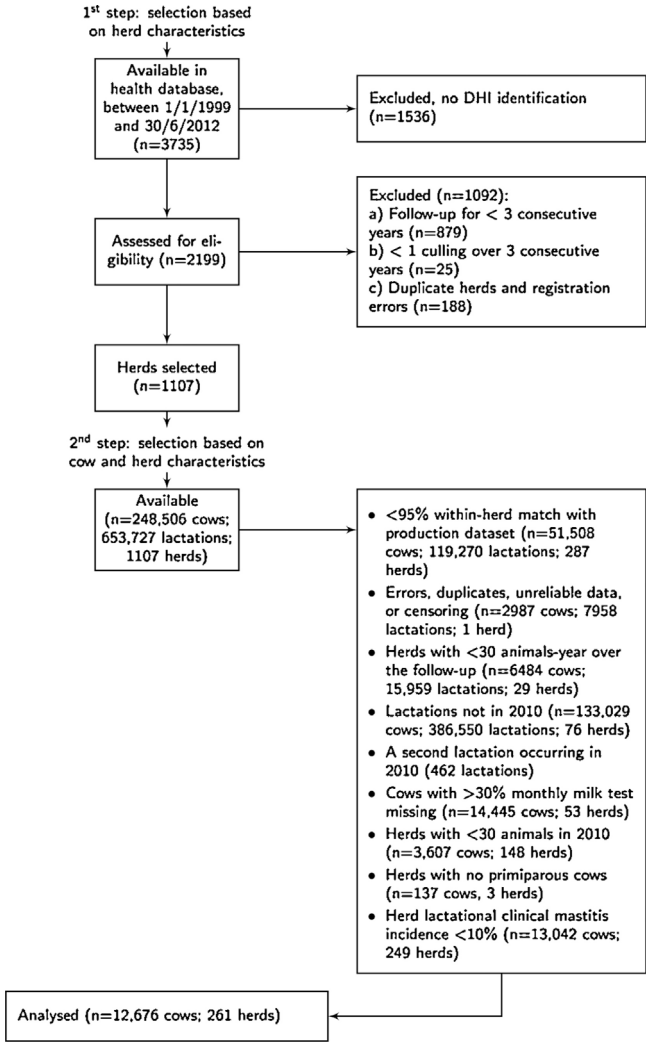

Fig. 2. Flowchart of herds and cows selection.

centralized DSA database by the herd veterinarian, which is then validated. Vets are therefore closely involved in the diagnosis of the disease conditions, as well as their recording and reporting. A purposive sample was created by extracting data for all lactations starting between January 1st, 2001 and December 31st, 2010 (249,536 cows from 3735 herds), keeping herds that had a minimum of three consecutive years of follow-up with *DSA Laitier* and for which at least one culling was recorded over this follow-up (see flowchart in Fig. 2). From this dataset, we extracted data for all lactations starting between January 1st and December 31st, 2010. If a cow had two lactations during the year 2010, one of the two lactations was randomly kept. Production data were obtained from the unique Québec dairy herd improvement (DHI) service provider (Valacta, Sainte-Anne-de-Bellevue, QC, Canada). Health and production data were matched based on herd- and cow-level identification. If not successful, further matching was tried, based on birth date, calving dates, and health and production history. Only herds for which at least 95% of the lactations from the health dataset could be matched with data from the production dataset were kept (42,809 cows from 714 herds). Herds with less than 30 animals, for which more than 30% of the DHI monthly tests were missing, and with a lactational cumulative incidence for CM in 2010 that was less than 10%, were removed. Cows with calving intervals, or an interval between the last calving and the end of data, longer than 580 days were censored at their last calving date. If this censoring was at their first calving date, the observation was dropped. Cows leaving their herd on their calving date were assigned one day of follow-up.

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