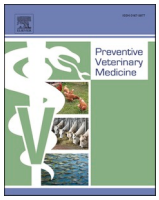
Preventive Veterinary Medicine 213 (2023) 105879

Contents lists available at ScienceDirect

Preventive Veterinary Medicine

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



# Association of pathogen-specific clinical mastitis in the first 100 days of first lactation with productive lifetime: An observational study comparing competing risks models for death and sale with the Cox model

Julia A. Hertl [a,*], Ynte H. Schukken [b,c], Loren W. Tauer [d], Francis L. Welcome [e,1], Yrjö T. Gröhn [a]

[a] Section of Epidemiology, Department of Population Medicine and Diagnostic Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853, United States
[b] Royal GD, 7418 EZ Deventer, the Netherlands
[c] Department of Animal Sciences, Wageningen University, 6700 AA Wageningen, the Netherlands
[d] Charles H. Dyson School of Applied Economics and Management, Cornell SC Johnson College of Business, Cornell University, Ithaca, NY 14853, United States
[e] Quality Milk Production Services, Department of Population Medicine and Diagnostic Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853, United States

ARTICLE INFO

*Keywords:*
Pathogen-specific mastitis
Cow productive lifetime
Survival analysis
Competing risks
Proportional subdistribution hazards model
Cox proportional hazards model

ABSTRACT

The objective of this observational study was to study the association between clinical mastitis (**CM**) (*Streptococcus* spp., *Staphylococcus aureus*, *Staphylococcus* spp., *Escherichia coli*, *Klebsiella* spp., cases with other treated or other not treated organisms, CM without growth) occurring in a dairy cow's first 100 days (**d**) of her first lactation and her total productive lifetime, ending in death or sale (for slaughter). Data were collected from 24,831 cows in 5 New York Holstein herds from 2004 to 2014. Two analytical approaches were compared. First, removals (death, sale) were treated as competing events in separate survival analyses, in proportional subdistribution hazards models. In one, death was coded as the event of interest and sale as the competing event; in another, sale was the event of interest and death the competing event. Second, traditional survival analysis (Cox proportional hazards) was conducted. In all models, the time variable was number of days from date of first calving until event (death or sale) date; if the cow was alive at study end, she was censored. Models were stratified by herd. Ten percent of cows died; 48.4 % were sold. In the competing risks analysis, *E. coli* and CM without growth were associated with death; the former with an increased hazard rate of death, the latter with a lower one. *Streptococcus* spp., *Staph. aureus*, *Klebsiella* spp., cases with other treated or untreated organisms, and CM without growth were associated with higher hazard rates of sale. The Cox proportional hazards model's hazard rates were higher than those in the competing risks model in which death was the event of interest, and resembled those in the model in which sale was the event of interest. Four additional Cox models, omitting dead or sold cows, or censoring each, were also fitted; hazard ratios were similar to the above models. Proportional subdistribution hazards models were appropriate due to competing risks (death, sale); they produce less-biased estimates. A study limitation is that while proportional subdistribution hazards models were appropriate, they have the illogical feature of keeping subjects at risk for the event of interest even after experiencing the competing event. This is, however, necessary in estimating cumulative incidence functions. Another limitation concerns pathogen variability among study farms, implying that CM decisions are farm-specific. Misclassification of 'dead' vs. 'sold' cows was also possible. Nevertheless, the findings may help in optimizing management of cows contracting specific types of CM early in productive lifetime.

*Abbreviations:* CM, Clinical mastitis; d, days; DIM, days in milk.

* Corresponding author.
*E-mail address:* jah12@cornell.edu (J.A. Hertl).

[1] Deceased; in memory of the many contributions of Dr. Frank Welcome.

https://doi.org/10.1016/j.prevetmed.2023.105879
Received 29 August 2022; Received in revised form 25 January 2023; Accepted 15 February 2023
Available online 18 February 2023

## 1. Introduction

Dairy cows spend on average 3–5 years producing milk and leave the herd for various reasons. These include low milk production (Gröhn et al., 2003; Olechnowicz and Jaśkowski, 2011), reproduction problems (Adamczyk et al., 2017; Armengol and Fraile, 2018), old age (Maher et al., 2008; Gussmann et al., 2019), and disease (Gröhn et al., 1998; Ansari-Lari et al., 2012). Shorter vs. longer productive lifetimes have advantages and disadvantages, depending on factors like herd size, cow performance (milk production, reproduction, udder health), health status, milk and meat prices, feed costs, and veterinary costs (Armengol and Fraile, 2018; DeVries, 2020). Superior genetics of the cow may lead to longer productive lifetime while an increase in the rate of genetic improvement can encourage earlier replacement. An objective of reducing dairy's impact on the environment may also result in fewer replacements and thus a longer productive lifetime (DeVries, 2020).

The term 'culling' may refer to death or sale of the cow, or both, depending on the study. Combining death and culling in a single event code, even though different processes cause these events, can lead to confusion (Armengol and Fraile, 2018) and biased estimates. Fetrow et al. (2006) advocate the term "herd turnover rate", which they define as the number of cows leaving the herd (for any reason) in a time period divided by the animal time at risk for the herd. This would be appropriate if information on specific reasons for herd exit, such as death or sale, are unavailable.

Traditional survival analysis measures time to a single event of interest, e.g., time to death from one cause, but does not consider death from another. Fine and Gray (1999) developed an extension of the Cox proportional hazards model (Cox, 1972), the proportional subdistribution hazards model, to account for such "competing risks". As far as the end of a cow's time in the herd (i.e., productive lifetime) is concerned, the death of a cow and the sale of a cow are competing events: once one occurs, the other is no longer possible. In the presence of competing events, Gondara (2015), concurring with Austin et al. (2016), demonstrated that hazard ratio estimates are biased upwards in the standard Cox (1972) model, which does not account for competing events, when compared with the Fine-Gray (1999) subdistribution model, which does account for competing events.

The competing risks approach may be used in a variety of contexts, even in what might be considered a single event. A cow may be sold for a variety of reasons, or even a combination of reasons, such as low production or disease. Moreover, even if a cow does not have low milk production, she may be replaced by a new, potentially more profitable cow. Cows may also be sold because the slaughter price for dairy beef is high. We presumed that sold animals were slaughtered for beef, rather than being sold to another farm to continue milking.

De Oliveira et al. (2020) used competing risks to study metritis treatments and hazards of being culled vs. conceiving in dairy cows. Chitosan microparticles had adverse effects on fertility and culling. Cows receiving ceftiofur had improved fertility, but increased culling. Pattamanont et al. (2021) also looked at the competing risks of culling and pregnancy in dairy cows, with their interest being dry period length in the previous lactation. They compared a cause-specific hazards model and a subdistribution model. Shorter dry periods were associated with lower culling risk early in the subsequent lactation, and with a higher pregnancy hazard. Both approaches produced similar hazard ratios.

Clinical mastitis (**CM**) has been a scourge to the dairy industry for decades. It has adverse effects on milk yield (Reksen et al., 2007; Hertl et al., 2014a), reproduction (Santos et al., 2004; Hertl et al., 2014b), and productive lifetime (Hertl et al., 2018; Gussmann et al., 2019), the focus of this study. Freebern et al. (2020), in a study on genetics, reported some association between mastitis and cow liveability. McConnel et al. (2018) developed a "Disability-Adjusted Life Year" metric for mastitis, to estimate time lost to it and to death. Effects of CM on productive lifetime vary with etiology. Particularly, *Klebsiella* spp. (Cha et al., 2013) and *Staphylococcus aureus* (Vakkamäki et al., 2017) were associated with a high rate of herd removal.

Few studies have examined the impact of CM, much less its etiology, occurring at the start of a cow's productive life on her lifespan, or on a cow's likelihood of dying vs. being sold. According to the International Dairy Federation (IDF, 2011), "early lactation" comprises the first 100 days (**d**) of a cow's lactation. The motivation for the current study was to investigate whether CM occurring during the earliest phase of a cow's productive life was associated with lifetime herd removal, whether through death or sale. Other researchers have studied alternative early lactation periods, although none used a competing risks model. Haine et al. (2017) studied effects of CM occurring in the first 120 d of lactation, in cows of all parities. Moussavi et al. (2012) studied CM occurring between first calving and 10 days in milk (**DIM**; i.e., days in lactation), 10–60 DIM, and after 60 DIM.

Gröhn et al. (2005) studied pathogens' effects throughout lactation on culling, and Cha et al. (2013) studied them on death and sale. More recently, Hertl et al. (2018) estimated the effect of CM occurring in the first 100 d of the first lactation on the length of a cow's productive lifetime. In that study, they did not look at the effect of different CM-causing pathogens, nor distinguish between death and sale as endpoints. In the current paper, we study the association of mastitis in early life with death and sale, recognizing that death and sale are clearly competing events.

This study also brings together several other features. The study period is a cow's full productive lifetime (rather than just one lactation). We include cases of pathogen-specific CM, occurring in the earliest stage of a cow's productive lifetime. Finally, we compare 2 analytical approaches: competing risks and the traditional Cox proportional hazards model. Our objective in this observational study was to estimate the association of these pathogens in CM cases occurring in the first 100 d in the first lactation of a dairy cow with her total productive lifetime, comparing the 2 analytical approaches.

## 2. Materials and methods

### 2.1. Data source

The dataset used in this study contained 24,831 cows in 5 New York State herds followed from 2004 to 2014. It was collected and reported in a previous study (Hertl et al., 2018). The herds were all conventionally managed, high-producing (305-d rolling herd average milk production ranged from 11,260 to 13,123 kg/cow per year) dairy herds, and had monthly mean somatic cell count ranging from 137,000 to 262,000 cells/ml.

Cows were housed in freestalls and were managed in groups according to lactation month, production, and reproduction status. They were fed balanced total mixed rations and were milked thrice daily.

Data on calving, milk production, reproduction, and other events, including death or culling (cows experiencing one of these events were denoted respectively as 'died' or 'sold' by the farm personnel), were obtained from DairyComp305 herd management software (Valley Agricultural Software, Tulare, CA). These data were then cleaned, edited, and output to a form suitable for analysis.

### 2.2. Cow eligibility

All 24,831 cows were followed from the date of their first calving until death, sale, or end-of-study date (4 February 2014). Cows still alive on the end-of-study date were right-censored, i.e., they had not experienced an event of interest (death or sale) before that date. While the independent variable of interest was CM occurring in the first 100 d of first lactation, some cows exited the herd before 100 d. They were, however, still included in the analyses.

### 2.3. Case identification and treatment

Clinical mastitis cases were recorded between January 2004 and February 2014. Milkers were instructed about the diagnosis of CM. They observed most cases when examining fore-stripped milk right before milking. A warm, swollen udder or change in milk consistency frequently occurred. Some cows had a sharp drop in milk yield (<70 % of the average of the previous 10 d) or rise in milk conductivity (>115 % of the average of the previous 10 d). Such cows were examined in further detail; if abnormal milk or a painful or swollen quarter was observed, CM was tentatively diagnosed with further testing. The microbiological diagnosis procedures are described in detail in Gröhn et al. (2004).

Farm-specific treatment protocols were present on each farm. The cows were assigned treatment and management protocols based on their clinical signs and causative pathogen. Details may be found in Cha et al. (2014). Clinical mastitis cases could have the following signs: Mild: abnormal milk (watery, flakes, fibrin clots, etc.); Moderate: abnormal milk and swollen or painful quarter; Severe: abnormal milk, swollen/-painful quarter, and systemic signs of illness (fever, reduced appetite, dehydration, etc.). Bacteriological culture was based on the farm protocol. In principle, all cases of CM were submitted for bacteriological culture to one of 3 laboratories in New York State in its 24-hour culture program. In this program that was run on a limited number of larger dairies, samples were collected daily and reported back to the farm within 24 h of pick-up. Final results were reported within 48 h. Cows may on occasion have been missed due to omissions of milkers or managers or results delayed due to inclement weather.

### 2.4. Case definition

The etiologies of interest were categorized into 8 groups: *Streptococcus* spp. (including *Strep. dysgalactiae*, *Strep. uberis*, and other *Streptococcus* spp.), *Staphylococcus aureus*, *Staphylococcus* spp., *Escherichia coli*, *Klebsiella* spp., CM cases with no important growth, other treated organisms (including *Corynebacterium bovis*, *Enterococcus*, *Pasteurella*, *Pseudomonas*, and other (unspecified) treated organisms), and other not treated organisms (including *Mycoplasma*, *Trueperella pyogenes*, and Yeast).

If a second CM case occurred in the same quarter within 5 d after the first case with either the same or a different pathogen, or within 14 d after the first one with the same pathogen, it was considered to be the same case. A case occurring in the same quarter 6–14 d after the first case, but with a different pathogen, was considered to be a new case. A case occurring more than 14 d after the previous case, with either the same or a different pathogen, was also considered to be a new case (Barkema et al., 1998). A case occurring in a different quarter from the previous case, regardless of the time interval between them or the pathogen(s) in both, was always considered a new case.

### 2.5. Statistical analysis

We used Fine and Gray's (1999) proportional subdistribution hazards model to estimate the association between the number of cases of the 8 different CM etiologies occurring in the first 100 d of first lactation (and average daily milk production of a cow), and a cow's hazard of dying or being sold, or herd exit overall, with the PHREG procedure in SAS (version 9.4; SAS Institute Inc., Cary, NC). In the subdistribution (or cumulative incidence function) hazards model, presence of competing events is accounted for by subject- and time-specific weights when censoring occurs (Gondara, 2015). Subjects not experiencing the event of interest or a competing event by time $t$ have equal weights. Subjects that do experience a competing event before time $t$ are assigned weights that are a function of the probability of still being followed at each time point $i$ (Gondara, 2015). The weights, which utilize the Kaplan-Meier estimate of the survival function of the censoring variable, decrease gradually over time, in relation to the conditional probability of still being followed if the subject had not experienced a competing event (SAS Institute, 2017). If the cow did not experience one of the events (death or sale), i.e., remained alive and in the herd at the end of the study, she was censored. The cow was the unit of analysis in this study.

In the standard Cox proportional hazards model, i.e., when competing risks are not accounted for, the hazard function is expressed as

$$\lambda(t) = \lim_{\Delta t \to 0} \frac{Prob(t \leq T < t + \Delta t | T \geq t)}{\Delta t} \quad (1)$$

where $t$ denotes specific event times and $T$ is time until an event of interest occurs (Austin et al., 2016).

In contrast, "Fine and Gray's (1999) proportional subdistribution hazards model" accounts for competing risks. This "subdistribution" is also known as the "cumulative incidence function". It is expressed as

$$\lambda_k^{sd}(t) = \lim_{\Delta t \to 0} \frac{Prob(t < T \leq t + \Delta t, D = k | T > t \cup (T < t \cap K \neq k))}{\Delta t} \quad (2)$$

where sd is the subdistribution under event k, where $t$ again denotes specific event times, and $T$ is time until an event of interest. Variable $D$ is event type, $1 \ldots k$ are the competing causes of failure, and the random variable $K$ denotes the competing causes of failure. Importantly, the risk set includes both subjects that have not yet experienced an event and subjects that have already had a competing event (Austin et al., 2016). After a competing event occurs, the subject remains (artificially) in the risk set, and is assigned decreasing weights at each timepoint for the remainder of the study period (Fig. 2 in Gondara, 2015); the weights are a function of the conditional probability of still being followed if they had not experienced the competing event (SAS Institute, 2017).

For the competing risks analyses, we analyzed 2 separate versions of the dataset, one with death as the event of interest and sale as the competing event, and the other with sale as the event of interest and death as the competing event. Eq. 2 was used for both analyses. The datasets were otherwise identical with data from all 24,831 cows, but with a difference in SAS coding of the variable to represent herd exit and the alternative censoring events ("CENSOR"; using the EVENTCODE option in the MODEL statement). In the dataset with death as the event of interest, the coding was censor = 0 for live cows (i.e., still alive on the end-of-study date (4 February 2014)), censor = 1 for dead cows, and censor = 2 for sold cows. In the dataset with sale as the event of interest, censor = 0 for live cows, censor = 1 for sold cows, and censor = 2 for dead cows.

For the traditional survival analysis with the Cox proportional hazards model, we also used the dataset with 24,831 cows. In this version, censor = 0 for live cows, and censor = 1 for cows that exited the herd, either through death or sale. All other variables were the same as in the 2 datasets used in the competing risks analyses.

In all 3 datasets, the time variable was the number of days from date of first calving until an event date (either sale or death) or censoring date (i.e., end-of-study date (4 February 2014)) if the cow was still alive. To account for herd-specific management protocols, all models were stratified by herd with additional separate analyses for the above models run for each farm. Model estimates were considered to be statistically significant at $\alpha = 0.05$. To assess the models' goodness of fit, the − 2 log likelihood values of each model, with and without the covariates (number of cases of each pathogen group occurring in the first 100 d of first lactation, and average daily milk production of a cow), were compared, with the likelihood ratio test.

Table 1 shows some of the variables used in the 3 analyses, for 10 example cows.

The LIFETEST procedure in SAS (version 9.4), with the LIFETABLE method, was used to estimate survival proportions and life expectancy, and to produce survival graphs, for each pathogen separately, and 'died', 'sold', and 'herd exit' (comprising both death and sale) outcomes separately. The analyses were stratified by number of cases of each

**Table 1**
Data layout for 10 example cows to study the effect of pathogen-specific clinical mastitis (CM)[a] occurring in the first 100 d of the first lactation on length of productive lifetime[b] in 24,831 cows in 5 New York State farms, followed from January 2004 until February 2014. The final 3 columns highlight the differences between the analytical approaches under study (competing risks models with death as event of interest and sale as event of interest, and the traditional Cox proportional hazards model, respectively).

| | Number of CM cases in first 100 d of first lactation due to: | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Cow ID | *Streptococcus* spp. | *Staphylococcus aureus* | *Escherichia coli* | Length of productive lifetime (d) | Event | Censor (in dataset where death is event of interest, and sale is competing event) | Censor (in dataset where sale is event of interest, and death is competing event) | Censor (in dataset where herd exit (death or sale) is event; Cox model) |
| 1 | 0 | 0 | 0 | 1418 | Alive[c] | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 | 989 | Died | 1 | 2 | 1 |
| 3 | 1 | 0 | 0 | 552 | Alive | 0 | 0 | 0 |
| 4 | 0 | 0 | 1 | 1201 | Died | 1 | 2 | 1 |
| 5 | 0 | 1 | 1 | 345 | Alive | 0 | 0 | 0 |
| 6 | 2 | 0 | 0 | 673 | Sold | 2 | 1 | 1 |
| 7 | 1 | 1 | 1 | 832 | Sold | 2 | 1 | 1 |
| 8 | 1 | 2 | 1 | 472 | Sold | 2 | 1 | 1 |
| 9 | 0 | 3 | 0 | 563 | Alive | 0 | 0 | 0 |
| 10 | 2 | 1 | 3 | 112 | Sold | 2 | 1 | 1 |

[a] Eight pathogen groups were included as predictors in the models; only 3 are shown here.
[b] Productive lifetime: number of days from date of first calving until death or sale in that or a subsequent lactation, or, if still alive, until end-of-study date (4 February 2014).
[c] Still alive at end-of-study (4 February 2014).

**Table 2**
Number (and percent) of cows that were alive, died, and were sold, and had clinical mastitis, by etiology, in first 100 d of first lactation, in 24,831 cows in 5 New York State Holstein dairy herds, followed from 2004 to 2014.

| | Farm | | | | | |
|---|---|---|---|---|---|---|
| | A (n = 6309 cows) | B (n = 2545 cows) | C (n = 6981 cows) | D (n = 5802 cows) | E (n = 3194 cows) | All (n = 24,831 cows) |
| Number (%) of cows alive | 2575 (40.8) | 966 (38.0) | 3232 (46.3) | 2122 (36.6) | 1496 (46.8) | 10,391 (41.9) |
| Number (%) of cows that died | 483 (7.7) | 139 (5.5) | 665 (9.5) | 831 (14.3) | 314 (9.8) | 2432 (9.8) |
| Number (%) of cows sold | 3251 (51.5) | 1440 (56.6) | 3084 (44.2) | 2849 (49.1) | 1384 (43.3) | 12,008 (48.4) |
| Number of cases in first 100 d of first lactation | # of cows (% on each farm) with n cases in 1st 100 d of lactation 1[a] | | | | | |
| *Streptococcus* spp.[b] | | | | | | |
| 0 | 6103 (96.7 %) | 2505 (98.4 %) | 6937 (99.4 %) | 5648 (97.4 %) | 3122 (97.8 %) | 24,315 (97.9 %) |
| 1 | 183 (2.9 %) | 34 (1.3 %) | 35 (0.5 %) | 147 (2.5 %) | 68 (2.1 %) | 467 (1.9 %) |
| 2 or more | 23 (0.4 %) | 6 (0.2 %) | 9 (0.1 %) | 7 (0.1 %) | 4 (0.1 %) | 49 (0.2 %) |
| *Staphylococcus aureus* | | | | | | |
| 0 | 6273 (99.4 %) | 2538 (99.7 %) | 6960 (99.7 %) | 5730 (98.8 %) | 3181 (99.6 %) | 24,682 (99.4 %) |
| 1 | 36 (0.6 %) | 6 (0.2 %) | 21 (0.3 %) | 68 (1.2 %) | 13 (0.4 %) | 144 (0.6 %) |
| 2 | 0 (0.0 %) | 1 (0.04 %) | 0 (0.0 %) | 4 (0.1 %) | 0 (0.0 %) | 5 (0.02 %) |
| *Staphylococcus* spp. | | | | | | |
| 0 | 6253 (99.1 %) | 2525 (99.2 %) | 6973 (99.9 %) | 5731 (98.8 %) | 3151 (98.7 %) | 24,633 (99.2 %) |
| 1 | 55 (0.9 %) | 20 (0.8 %) | 8 (0.1 %) | 67 (1.2 %) | 42 (1.3 %) | 192 (0.8 %) |
| 2 | 1 (0.02 %) | 0 (0.0 %) | 0 (0.0 %) | 4 (0.1 %) | 1 (0.03 %) | 6 (0.02 %) |
| *Escherichia coli* | | | | | | |
| 0 | 6159 (97.6 %) | 2518 (98.9 %) | 6885 (98.6 %) | 5665 (97.6 %) | 3141 (98.3 %) | 24,368 (98.1 %) |
| 1 | 148 (2.4 %) | 27 (1.1 %) | 93 (1.3 %) | 129 (2.2 %) | 53 (1.7 %) | 450 (1.8 %) |
| 2 | 2 (0.03 %) | 0 (0.0 %) | 3 (0.04 %) | 8 (0.1 %) | 0 (0.0 %) | 13 (0.1 %) |
| *Klebsiella* spp. | | | | | | |
| 0 | 6284 (99.6 %) | 2542 (99.9 %) | 6976 (99.9 %) | 5781 (99.6 %) | 3152 (98.7 %) | 24,735 (99.6 %) |
| 1 | 24 (0.4 %) | 3 (0.1 %) | 5 (0.1 %) | 21 (0.4 %) | 41 (1.3 %) | 94 (0.4 %) |
| 2 | 1 (0.02 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 1 (0.03 %) | 2 (0.01 %) |
| No Growth | | | | | | |
| 0 | 6125 (97.1 %) | 2503 (98.4 %) | 6945 (99.5 %) | 5599 (96.5 %) | 3066 (96.0 %) | 24,238 (97.6 %) |
| 1 | 173 (2.7 %) | 41 (1.6 %) | 35 (0.5 %) | 191 (3.3 %) | 115 (3.6 %) | 555 (2.2 %) |
| 2 or more | 11 (0.2 %) | 1 (0.04 %) | 1 (0.01 %) | 12 (0.2 %) | 13 (0.4 %) | 38 (0.2 %) |
| Other Treated Organisms[c] | | | | | | |
| 0 | 6031 (95.6 %) | 2522 (99.1 %) | 6962 (99.7 %) | 5758 (99.2 %) | 3154 (98.8 %) | 24,427 (98.4 %) |
| 1 | 282 (3.7 %) | 22 (0.9 %) | 18 (0.3 %) | 42 (0.7 %) | 36 (1.1 %) | 350 (1.4 %) |
| 2 or more | 46 (0.7 %) | 1 (0.04 %) | 1 (0.01 %) | 2 (0.03 %) | 4 (0.1 %) | 54 (0.2 %) |
| Other Not Treated Organisms[d] | | | | | | |
| 0 | 6250 (99.1 %) | 2516 (98.9 %) | 6951 (99.6 %) | 5780 (99.6 %) | 3172 (99.3 %) | 24,669 (99.4 %) |
| 1 | 58 (0.9 %) | 29 (1.1 %) | 29 (0.4 %) | 20 (0.3 %) | 21 (0.7 %) | 157 (0.6 %) |
| 2 | 1 (0.02 %) | 0 (0.0 %) | 1 (0.01 %) | 2 (0.03 %) | 1 (0.03 %) | 5 (0.02 %) |

[a] Percentages may not add up exactly to 100 %, due to rounding.
[b] Includes *Strep. dysgalactiae* (total n = 206), *Strep. uberis* (n = 85), and other (unspecified) *Streptococcus* spp. (n = 225).
[c] Includes *Corynebacterium bovis* (n = 18), *Enterococcus* (n = 1), *Pasteurella* (72), *Pseudomonas* (3), and other (unspecified) treated organisms (n = 310).
[d] Includes *Mycoplasma* (n = 19), *Trueperella pyogenes* (n = 85), and Yeast (n = 58).

pathogen occurring in the first 100 d of first lactation.

As "sensitivity analyses", we fitted 4 additional Cox proportional hazards models (i.e., traditional survival analysis): (1). Only cows that died and cows that were alive were included; (2) Only cows that were sold and cows that were alive were included; (3) All cows were included, but those that were sold were also censored (so "died" was the only event); and (4) All cows were included, but those that died were also censored (so "sold" was the only event). Thus, (3) and (4) incorporate additional censoring, as well as the usual censoring for end-of-study.

## 3. Results

### 3.1. Pathogen occurrence in farms

Table 2 shows the numbers and percentages of cows in each farm, and overall, alive on end-of-study date (these cows were censored), dead, and sold, and that had one or more CM cases due to the different etiologies in the first 100 d of first lactation. Approximately 10 % of cows died with median (range) days in herd: 627 (1−2595), and nearly half were sold with median (range) days in herd: 705 (3−3363), during the study period. Some cows (n = 1995) exited the herd in the first 100 d (but were still included in the analyses). Approximately 10 % of the cows had at least one CM case in the first 100 d of first lactation. Overall, the most common types of early-occurring CM were cases with no growth, *Streptococcus* spp., and *E. coli*.

### 3.2. Competing risks model: early-life pathogen-specific clinical mastitis and subsequent death

#### 3.2.1. Association of early-life pathogen-specific CM and death

Table 3 shows hazard ratios and their 95 % confidence intervals for the association of cases of pathogens occurring in the first 100 d of first lactation with length of productive lifetime, from a proportional subdistribution hazards model in which death was the event of interest and sale was the competing event. Clinical mastitis cases with *E. coli* occurring in the first 100 d of first lactation were associated with a higher hazard rate of death (1.32; $P = 0.0384$) (Table 3). In contrast, CM cases with no growth then were associated with a lower hazard rate of death (0.66; $P = 0.0092$). Average daily milk production in a cow's productive lifetime was associated with a small increased risk of death ($P < 0.0001$).

**Table 3**
Hazard ratios, 95 % confidence intervals (CIs), and *P*-values for early-occurring[a] clinical mastitis pathogens' effects on length of productive lifetime, in 24,831 cows in 5 New York State Holstein dairy herds, from 2004—2014, from a proportional subdistribution hazards model using a competing risks approach: death is the event of interest and sale is the competing event. Cows still alive at end-of-study (4 February 2014) were censored. The data were stratified by herd.[b]

| Pathogen | Number of cases in first 100 d of first lactation | Hazard Ratio | 95 % CI for Hazard Ratio | *P*-value |
|---|---|---|---|---|
| *Streptococcus* spp. | 0 (reference level) | 1.0 | – | |
| | 1 | 0.95 | 0.68, 1.31 | 0.7316 |
| | 2 or more | 1.09 | 0.45, 2.62 | 0.8493 |
| *Staphylococcus aureus* | 0 | 1.0 | – | |
| | 1 or more | 0.75 | 0.43, 1.32 | 0.3222 |
| *Staphylococcus* spp. | 0 | 1.0 | – | |
| | 1 or more | 0.99 | 0.62, 1.58 | 0.9693 |
| *Escherichia coli* | 0 | 1.0 | – | |
| | 1 or more | 1.32 | 1.02, 1.71 | 0.0384 |
| *Klebsiella* spp. | 0 | 1.0 | – | |
| | 1 or more | 0.84 | 0.43, 1.64 | 0.6146 |
| No growth | 0 | 1.0 | – | |
| | 1 or more | 0.66 | 0.49, 0.90 | 0.0092 |
| Other treated organisms | 0 | 1.0 | – | |
| | 1 or more | 0.95 | 0.66, 1.37 | 0.7682 |
| Other not treated organisms | 0 | 1.0 | – | |
| | 1 or more | 1.22 | 0.74, 2.03 | 0.4310 |

[a] First 100 d of first lactation.
[b] Average daily milk production in a cow's productive lifetime was also included in the model (hazard ratio = 1.02; $P < 0.0001$).

Within the 5 individual farms (results within each farm not shown), there were associations between early-occurring *Staph. aureus*, *E. coli*, and cases with no growth and a higher hazard of death only in Farm A. Early-occurring *Streptococcus* spp. was associated with a higher hazard of death in Farm C, while cases with no growth were associated with a lower hazard of death in Farm D.

Survival curves for cows that died and those still alive on the end-of-study date, stratified by number of cases of each pathogen occurring in the first 100 d of first lactation, for all farms together, are presented in Fig. 1.

#### 3.2.2. Model fit (death as event of interest)

The null model's − 2 × log likelihood value was 39,898.66. Adding the 8 pathogens (9 DF: 2 DF for *Streptococcus* spp. and 1 DF each for the other 7 pathogens) and milk production reduced it to 39,813.94, resulting in an improvement in fit (likelihood ratio chi-square on 10 DF was 84.72 ($P < = 0.001$)).

### 3.3. Competing risks model: early-life pathogen-specific clinical mastitis and subsequent sale

#### 3.3.1. Association of early-life pathogen-specific CM and sale

Table 4 shows hazard ratios and their 95 % confidence intervals for the associations of cases of pathogens occurring in the first 100 d of first lactation with length of productive lifetime, from a proportional subdistribution hazards model in which sale was the event of interest and death was the competing event. *Streptococcus* spp. CM occurring in the first 100 d of productive lifetime was associated with sale; having one case then was associated with a 1.3 times higher hazard rate of sale ($P < 0.0001$), while having 2 or more cases was associated with a 1.7 times higher hazard rate ($P = 0.0083$) (Table 4). Early-occurring *Staph. aureus*, *Klebsiella* spp., cases due to other treated or not treated organisms, and cases with no growth were also associated with later sale (all $P < 0.006$). Average daily milk production in a cow's productive lifetime was associated with a small increased risk of sale ($P < 0.0001$).

Within the 5 individual farms (results within each farm not shown), there were associations between early-occurring cases of all pathogens, except for *E. coli*, and a higher hazard of sale in several farms.

Survival curves for cows that were sold and those still alive at the end of the study, stratified by number of cases of each pathogen occurring in the first 100 d of first lactation, for all farms together, are presented in Fig. 2.

#### 3.3.2. Model fit (sale as event of interest)

The null model's − 2 × log likelihood value was 186,377.23. Adding the 8 pathogens (9 DF: 2 DF for *Streptococcus* spp. and 1 DF each for the other 7 pathogens) and milk production reduced it to 186,007.53, resulting in an improvement in fit (likelihood ratio chi-square on 10 DF was 369.7 ($P < 0.001$)).

### 3.4. Cox proportional hazards model: early-life pathogen-specific clinical mastitis and subsequent herd exit

#### 3.4.1. Association of early-life pathogen-specific CM and herd exit

Table 5 shows hazard ratios and their 95 % confidence intervals for the associations of cases of pathogens occurring in the first 100 d of first lactation with length of productive lifetime, from a Cox proportional hazards model, in which herd exit (either through death or sale) was the event. *Streptococcus* spp. CM occurring in the first 100 d of productive lifetime was associated with herd exit; having one case then was associated with a 1.3 times higher hazard rate of exit ($P < 0.0001$), while

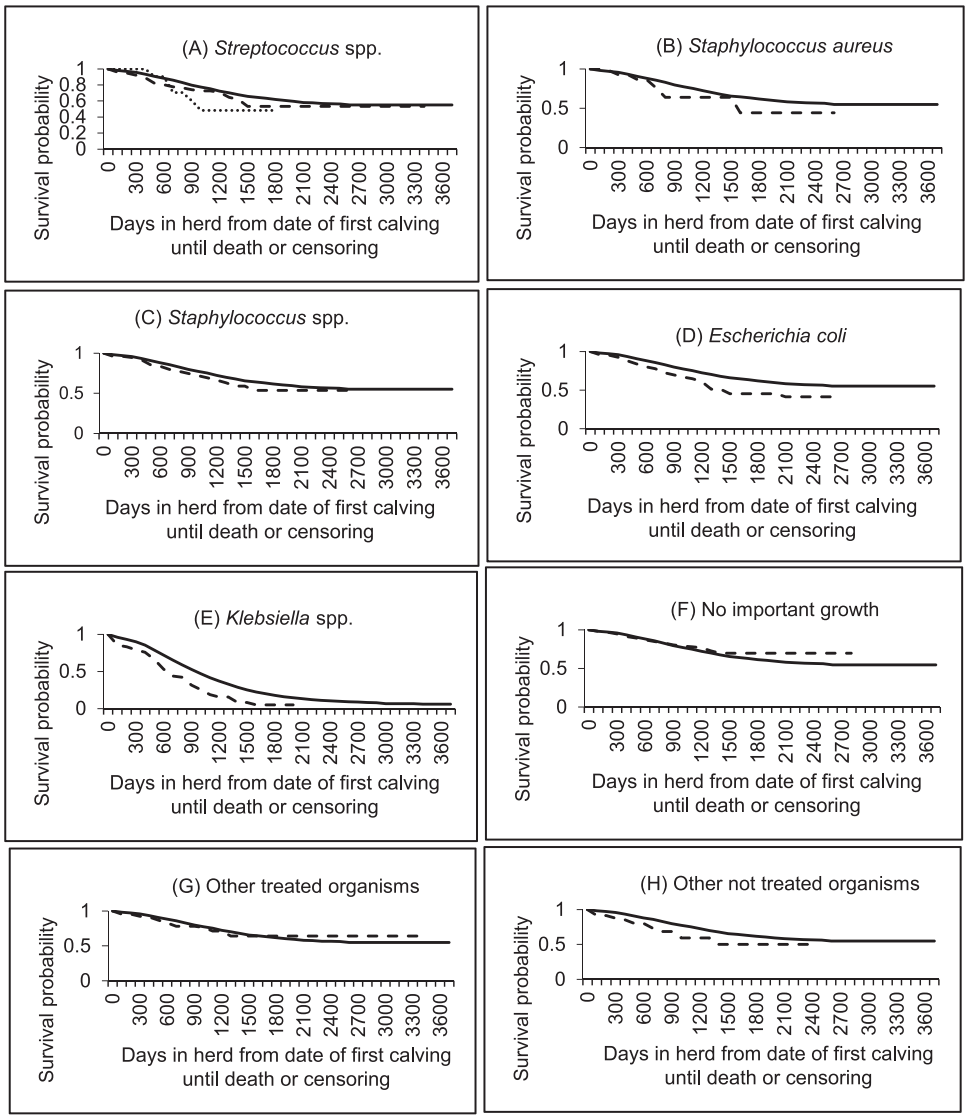



**Fig. 1.** Survival curves stratified by number of clinical mastitis (CM) cases (0: solid line; 1 or more: dashed line; 2 or more cases (*Streptococcus* spp. only): dotted line), by etiology, occurring in first 100 d of first lactation, in 12,823 cows (died (n = 2432) or still alive (n = 10,391)) in 5 New York State dairy herds, followed from 2004 until 2014. (A) *Streptococcus* spp. (including *Strep. dysgalactiae*, *Strep. uberis*, and other *Streptococcus* spp.), (B) *Staphylococcus aureus*, (C) *Staphylococcus* spp., (D) *Escherichia coli*, (E) *Klebsiella* spp., (F) CM cases with no important growth, (G) Other treated organisms (including *Corynebacterium bovis*, *Enterococcus*, *Pasteurella*, *Pseudomonas*, and other (unspecified) treated organisms), and (H) Other not treated organisms (including *Mycoplasma*, *Trueperella pyogenes*, and Yeast).

having 2 or more cases was associated with a 1.8 times higher hazard rate ($P = 0.0002$) (Table 5). Early-occurring *Staph. aureus*, *E. coli*, *Klebsiella* spp., cases due to other treated or not treated organisms, and cases with no growth were also associated with herd exit (all $P < 0.0013$). Average daily milk production in a cow's productive lifetime was associated with a small increased risk of herd exit ($P < 0.0001$).

Within the 5 individual farms (results within each farm not shown), there were associations between early-occurring cases of all pathogens, except for *Staphylococcus* spp., and a higher hazard of herd exit in most farms. There was an association between *Staphylococcus* spp. and a lower hazard of herd exit in Farm D.

Survival curves for cows that exited the herd, either through death or sale, and those still alive at the end of the study, stratified by number of cases of each pathogen occurring in the first 100 d of first lactation, for all farms together, are presented in Fig. 3.

#### 3.4.2. Model fit

The null model's −2 × log likelihood value was 204,587.44. Adding the 8 pathogens (9 DF: 2 DF for *Streptococcus* spp. and 1 DF each for the other 7 pathogens) and milk production reduced it to 203,929.01, resulting in an improvement in fit (likelihood ratio chi-square on 10 DF was 658.43 ($P < 0.001$)).

### 3.5. Sensitivity analyses

#### 3.5.1. Inclusion of only live and dead cows

This dataset contained 12,823 cows (2432 dead cows and 10,391 cows still alive at end-of-study). The live cows were censored; sold cows were omitted. Table 6 (left-hand side) shows hazard ratios for the effects of pathogen-specific CM occurring in the first 100 d of first lactation on productive lifetime (with death as the only event of interest), in a Cox proportional hazards model. *Streptococcus* spp., *E. coli*, and other not treated organisms were associated with higher hazard rates of death. These hazard rates were higher than those in Table 3 (where death was the event of interest in the competing risks model).

#### 3.5.2. Inclusion of only live and sold cows

This dataset contained 22,399 cows (12,008 sold cows and 10,391 cows still alive at end-of-study). The live cows were censored; dead cows were omitted. Table 6 (right-hand side) shows hazard ratios for the effects of pathogen-specific CM occurring in the first 100 d of first lactation on productive lifetime (with sale as the only event of interest), in a Cox proportional hazards model. All pathogens except for *Staphylococcus* spp. were associated with higher hazard rates of sale. These hazard rates were generally higher than those in Table 4 (where death was the event of interest in the competing risks model).

**Table 4**
Hazard ratios, 95 % confidence intervals (CIs), and *P*-values for early-occurring[a] clinical mastitis pathogens' effects on length of productive lifetime, in 24,831 cows in 5 New York State Holstein dairy herds, from 2004—2014, from a proportional subdistribution hazards model using a competing risks approach: sale is the event of interest and death is the competing event. Cows still alive at end-of-study (4 February 2014) were censored. The data were stratified by herd.[b].

| Pathogen | Number of cases in first 100 d of first lactation | Hazard Ratio | 95 % CI for Hazard Ratio | *P*-value |
|---|---|---|---|---|
| *Streptococcus* spp. | 0 (reference level) | 1.0 | – | |
| | 1 | 1.34 | 1.17, 1.53 | < 0.0001 |
| | 2 or more | 1.72 | 1.15, 2.57 | 0.0083 |
| *Staphylococcus aureus* | 0 | 1.0 | – | |
| | 1 or more | 1.60 | 1.25, 2.03 | 0.0002 |
| *Staphylococcus* spp. | 0 | 1.0 | – | |
| | 1 or more | 1.00 | 0.81, 1.23 | 0.9912 |
| *Escherichia coli* | 0 | 1.0 | – | |
| | 1 or more | 1.13 | 0.99, 1.29 | 0.0744 |
| *Klebsiella* spp. | 0 | 1.0 | – | |
| | 1 or more | 1.55 | 1.17, 2.05 | 0.0024 |
| No growth | 0 | 1.0 | – | |
| | 1 or more | 1.42 | 1.27, 1.60 | < 0.0001 |
| Other treated organisms | 0 | 1.0 | – | |
| | 1 or more | 1.25 | 1.07, 1.47 | 0.0057 |
| Other not treated organisms | 0 | 1.0 | – | |
| | 1 or more | 1.42 | 1.15, 1.75 | 0.0011 |

[a] First 100 d of first lactation.
[b] Average daily milk production in a cow's productive lifetime was also included in the model (hazard ratio = 1.02; $P < 0.0001$).

#### 3.5.3. Inclusion of all cows (sold cows also censored)

This dataset contained all 24,831 cows, but sold cows were also censored, so death was the only event of interest. In this Cox proportional hazards model (Table 7, left-hand side), only *E. coli* was associated with a higher hazard rate of death. It (1.38) was similar to the estimate in the competing risks model in which death was the event of interest (1.32; Table 3), and slightly higher than the estimate in the Cox model in which both death and sale were events (1.20; Table 5).

#### 3.5.4. Inclusion of all cows (dead cows also censored)

This dataset contained all 24,831 cows, but dead cows were also censored, so sale was the only event of interest. In this Cox proportional hazards model (Table 7, right-hand side), all pathogens except for *Staphylococcus* spp. were associated with a higher hazard rate of sale. These estimates were generally higher than in the competing risks model in which sale was the event of interest (Table 4), and the estimates in the Cox model in which both death and sale were events (Table 5).

## 4. Discussion

### 4.1. Rationale for analytical approaches

Survival analysis is an appropriate method to study time to an event. When there are competing events, however, e.g., sale or death due to different causes, the traditional Cox proportional hazards model overestimates the individual hazards, because either event leads to exit from the herd. Therefore, a modified version should be applied (Austin et al., 2016). Two such versions, the cause-specific hazard function and the subdistribution hazard function (also known as the cumulative incidence function), may be used. The former estimates the instantaneous rate of occurrence of a particular event in subjects that have not yet experienced any events of any type. The latter estimates the instantaneous risk of failure from a particular event in subjects that have not yet had an event of that type (Austin et al., 2016), the model developed by Fine and Gray (1999).

When more than one event is possible, Allison (2018) advocated using the cause-specific hazards method (Kalbfleish and Prentice, 2002), rather than the Fine and Gray subdistribution hazards model. Allison's (2018) rationale against the latter is that when a subject experiences a competing event, it is no longer at risk of any other event, yet is still at risk of the event of interest in the Fine and Gray model. Fine and Gray (1999) agree that while this is not logical, their model is used to estimate the effects of factors on cumulative incidence functions, which can be used for prediction. The cause-specific hazards approach has its own drawbacks: if a subject is censored, their risk of an event is not known at the time of censoring; in some circumstances this lack of knowledge could result in bias (Allison, 2018). Thus, it would appear that there is no one "right" way to analyze survival data with competing events; the most appropriate may depend on the nature of the data and other considerations.

We assume that the death of a cow is involuntary culling. In the case of a cow with a bad prognosis and still within a long-term residue period due to a previous treatment, however, the farmer may decide to euthanize the animal rather than wait and cull. This would then represent a 'voluntary death'. In our analyses, we assume that such situations would be exceptions.

In this study, we used the subdistribution hazard function to estimate the association between early-occurring CM of different etiologies and the competing risks of death and sale in dairy cows. The current study, in accounting for the competing risks of death and sale, clearly distinguishes between these 2 types of exit from the herd. Given the important differences in mastitis as a risk factor for sale and death, we would argue that this distinction is biologically and epidemiologically relevant.

The current study features several different themes. First, the time period of interest is a cow's entire productive lifetime, from date of first calving until herd exit (whether through death or sale) or censoring (at end-of-study date (4 February 2014) if she is still in the herd then), rather than only one lactation. Second, we include cases of CM of different etiologies occurring in the earliest stage (first 100 d of first lactation) of a cow's productive lifetime, a period in which the cow is undergoing many changes, both within her body and becoming a productive member in the herd. Third, we compare 2 analytical approaches for survival analysis, Fine and Gray's (1999) proportional subdistribution hazards model, to account for the competing risks of death and sale, and the traditional Cox proportional hazards model (1972). All of these features provide a contribution to the field of dairy epidemiology.

### 4.2. Comparison with other studies

Abdel-Qadir et al. (2018) compared estimates on stroke hospitalization in humans with death due to other causes as the competing event using Cox and Fine-Gray methods. They found that the former overestimated the incidence of both stroke hospitalization and death without stroke. Feakins et al. (2018) also reported overestimates of risk from a standard survival model, compared with the Fine-Gray subdistribution hazard model, in a study of albuminuria in diabetic patients on cardiovascular and cancer mortality. In the current study, on CM in dairy cows, our Cox model produced higher hazard ratios than did the Fine and Gray model with death as the event of interest, but similar hazard ratios as the Fine and Gray model with sale as the event of interest. Therefore, farmers appear to preferably sell a cow before her health deteriorates from CM, leading to death.

In veterinary epidemiology few studies using competing risk methodology have been published; 2 examples involving dairy cows' reproduction and culling are De Oliveira et al. (2020) and Pattamanont et al. (2021). A number of different factors in Duroc sows, including year at first farrowing, and leg and hoof factors, among others, were risks for death or culling for low productivity or low fertility to varying degrees in competing risks analyses (De Sevilla et al., 2009). Dam age and type of

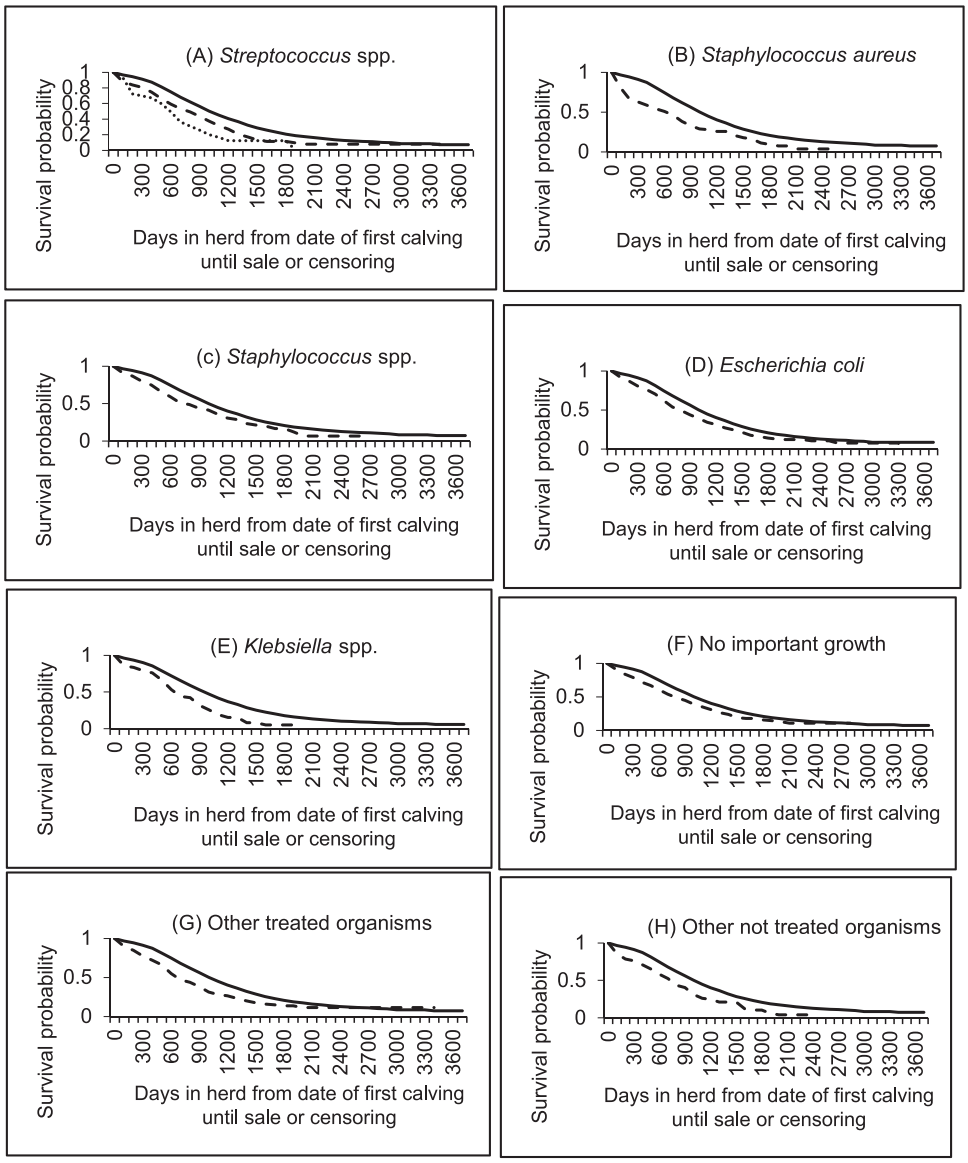



**Fig. 2.** Survival curves stratified by number of clinical mastitis (CM) cases (0: solid line; 1 or more: dashed line; 2 or more cases (*Streptococcus* spp. only): dotted line), by etiology, occurring in first 100 d of first lactation, in 22,399 cows (sold (n = 12,008) or still alive (n = 10,391)) in 5 New York State dairy herds, followed from 2004 until 2014. (A) *Streptococcus* spp. (including *Strep. dysgalactiae*, *Strep. uberis*, and other *Streptococcus* spp.), (B) *Staphylococcus aureus*, (C) *Staphylococcus* spp., (D) *Escherichia coli*, (E) *Klebsiella* spp., (F) CM cases with no important growth, (G) Other treated organisms (including *Corynebacterium bovis*, *Enterococcus*, *Pasteurella*, *Pseudomonas*, and other (unspecified) treated organisms), and (H) Other not treated organisms (including *Mycoplasma*, *Trueperella pyogenes*, and Yeast).

birth were risk factors for several causes of mortality (dam-related, pneumonia, other diseases, other causes) in lambs in a competing risks model (Southey et al., 2004). In a study of disposal reasons in Quebec dairy herds, Dürr et al. (1997) used cause-specific hazard functions to model competing risks of culling for low production, reproductive problems, mastitis, and other diseases and reasons. Maia et al. (2014) used bivariate competing risk genetic models to study death and slaughtering rates simultaneously in Danish cattle. To the best of our knowledge, no papers applying the competing risks approach to survival analysis in mastitis in dairy cows have been published.

In this study, we considered the terms "longevity" and "productive lifetime" to be the same. However, longevity might be defined in some studies as the time from birthdate to removal date, rather than date of first calving (start of productive lifetime) to removal date. Longevity can also be seen as the natural ability for cows to live. Productive lifetime may mean that a farmer made a decision to sell a cow. In the current study, it covered the entire time (including dry periods between lactations) that a cow was producing milk in the herd, with the end date either death (cow's ability to live) or sale (farmer's decision) (or censoring, if still alive on end-of-study date).

There are many studies on the effects of mastitis on bovine longevity/productive lifetime (e.g. Beaudeau et al., 1995; Haine et al., 2017; Gussmann et al., 2019), but few look at specific pathogens causing CM, or specifically on cases occurring in the earliest stage of productive lifetime. Gröhn et al. (2005) and Cha et al. (2013) have studied the effects of different pathogens on culling (the latter on death and sale separately), but not specifically occurring in early productive lifetime. Using time-dependent covariates for CM, Gröhn et al. (2005) found that the first occurrences of CM due to *Staphylococcus* spp., *E. coli*, *Klebsiella* spp., and *T. pyogenes* all had detrimental effects on productive lifetime; impacts varied depending on when in lactation these CM cases were diagnosed. In a later study, Cha et al. (2013) estimated the effects of first and repeated cases of pathogen-specific CM on mortality and culling. In first lactation cows, a first case of *E. coli* or *Klebsiella* spp. was particularly associated with a higher risk of mortality. Cases of *Staph. aureus*, *E. coli*, *Klebsiella* spp., and *T. pyogenes* in the first lactation increased the risk of culling.

Hagiwara et al. (2016) studied the association between acute *E. coli* mastitis and mortality in Japanese dairy cows. Several diagnostic parameters were useful in predicting which cows with *E. coli* would die or be euthanized. Among the risk factors were hematocrit and non-esterified fatty acid values, antithrombin activity, platelet counts, and presence of dysstasia (difficulty in standing). Silva and Costa (2001) reported on an outbreak of *Klebsiella pneumoniae* mastitis which resulted

**Table 5**
Hazard ratios, 95 % confidence intervals (CIs), and *P*-values for early-occurring[a] clinical mastitis pathogens' effects on length of productive lifetime, in 24,831 cows in 5 New York State Holstein dairy herds, from 2004—2014, from a traditional Cox proportional hazards model. The event of interest was removal from the herd (through either death or sale). Cows still alive at end-of-study (4 February 2014) were censored. The data were stratified by herd.[b]

| Pathogen | Number of cases in first 100 d of first lactation | Hazard Ratio | 95 % CI for Hazard Ratio | *P*-value |
|---|---|---|---|---|
| *Streptococcus* spp. | 0 (reference level) | 1.0 | – | |
| | 1 | 1.34 | 1.21, 1.53 | < 0.0001 |
| | 2 or more | 1.81 | 1.32, 2.48 | 0.0002 |
| *Staphylococcus aureus* | 0 | 1.0 | – | |
| | 1 or more | 1.49 | 1.23, 1.79 | < 0.0001 |
| *Staphylococcus* spp. | 0 | 1.0 | – | |
| | 1 or more | 0.95 | 0.80, 1.14 | 0.6005 |
| *Escherichia coli* | 0 | 1.0 | – | |
| | 1 or more | 1.20 | 1.07, 1.34 | 0.0013 |
| *Klebsiella* spp. | 0 | 1.0 | – | |
| | 1 or more | 1.55 | 1.23, 1.97 | 0.0003 |
| No growth | 0 | 1.0 | – | |
| | 1 or more | 1.33 | 1.20, 1.47 | < 0.0001 |
| Other treated organisms | 0 | 1.0 | – | |
| | 1 or more | 1.32 | 1.16, 1.50 | < 0.0001 |
| Other not treated organisms | 0 | 1.0 | – | |
| | 1 or more | 1.52 | 1.26, 1.82 | < 0.0001 |

[a] First 100 d of first lactation.
[b] Average daily milk production in a cow's productive lifetime was also included in the model (hazard ratio = 1.02; $P < 0.0001$).

in the deaths of 14 cows in a 104-cow dairy herd in Brazil. From these reported studies it may be concluded that coliform mastitis (*E. coli*, *Klebsiella* spp.), more than other pathogens, appears to be associated with greater mortality in dairy cows. Also in our data, only *E. coli* CM was associated with an increased risk of death.

Gussmann et al. (2019) conducted separate survival analyses in mid- and late-lactation heifers, and early-, mid-, and late-lactation cows. They found that the effect of mastitis differed depending on lactation stage. Pritchard et al. (2013), in a study of various traits in the first 3 lactations of British Holstein-Friesians, found a negative genetic correlation between mastitis and lifespan score.

Puerto et al. (2021) studied the effects of mastitis occurring in different stages of lactation (1–21 DIM, 22–100 DIM, 101–200 DIM, and 201 + DIM) on production and economic parameters, in mixed models. They found that mastitis occurring in the first 21 DIM and after 200 DIM had the greatest impact. The current study found CM occurring in the first 100 d (of the first lactation) was associated with sale, but not particularly with death. Puerto et al. (2021) also reported some differences between subsets of cows (those that were in the herd for at least 100 DIM, and those that were in the herd for at least 305 DIM). In contrast, our results were similar whether all cows were included in the analysis, or only cows that survived at least the first 100 d of their first lactation were included in the analysis (latter not shown). This implies that the association of CM with productive lifetime is not exclusively of brief duration; it appears to persist beyond the short-term.

Haine et al. (2017) fitted a marginal structural Cox model to account for time-varying exposures and covariates in estimating the effect of CM occurring in the first 120 d of lactation on subsequent culling in 12,676 cows in 261 Québec herds. First-lactation cows with CM in the first 120 DIM had a twice higher hazard of culling than did first-lactation cows that did not have CM in the first 120 DIM. In our study, hazard ratios for most of the pathogens in the competing risks model with sale as the event of interest and in the Cox model were somewhat lower (average = 1.4). In the Haine study, 15 % of first-lactation cows had one CM case in the first 120 DIM, while 1.5 % and 0.4 % of cows had 2 and 3 cases, respectively. These incidences (totaling roughly 17 %) are somewhat higher than those from our study where we observed approximately 10 % of first-lactation cows that had at least one CM case in the first 100 DIM. The Haine et al. (2017) study covered a slightly longer interval (120 d), which may account for some of the difference. Another reason for the difference may be different coding of events relating to herd exit.

In a study of 9183 first-lactation Holsteins, Moussavi et al. (2012) found that CM occurring between first calving and conception increased the risk of culling. Length of productive lifetime varied with DIM at the time of the first CM case. Survival curves were lowest for CM occurring in the first 10 DIM and 10–60 DIM, and somewhat higher for the first case occurring after 60 DIM. Seven percent of cows had one CM case and 1.5 % had 2 or more cases. More than one CM case was also associated with shorter productive lifetime. Similarly in our study, having at least one case of CM in early lactation (of the first lactation, specifically) was associated with a higher hazard of herd exit. Beaudeau et al. (2000) reviewed the effects of mastitis and other diseases on culling. In agreement with Moussavi et al. (2012), they reported that mastitis occurring before peak milk production, i.e. early in lactation, has a larger effect on culling than when CM occurs later in lactation. In an earlier study of French Holsteins, Beaudeau et al. (1995) found that cows with mastitis diagnosed before 45 DIM in their first lactation were 1.3 times more likely to be culled than cows without mastitis. This finding is comparable to the results from this study. Beaudeau et al. (1995) concluded that diseases occurring early in first lactation are detrimental to length of productive lifetime, particularly soon after the occurrence of CM: a sound reason to focus more attention on cows experiencing CM early in lactation.

### 4.3. Comments on study findings

Based on our previous work, we would expect that the same pathogens that are negatively associated with milk yield and reproduction, and positively associated with culling (within one lactation), namely Gram-negative organisms (*E. coli*, *Klebsiella* spp.), would also be negatively associated with productive lifetime. This was indeed the case, where *E. coli* was significantly associated with death but remarkably not significantly associated with sale. Some Gram-positive organisms (*Streptococcus* spp., *Staph. aureus*) were also associated with a reduced productive lifetime. As these were more associated with sale rather than with death, it may be that their detrimental effects accumulate over a longer planning horizon (beyond one lactation), possibly due to long-term effects on the mammary gland, scar tissue, and immune responsiveness, and are not associated with severe clinical signs.

The association between CM of different etiologies occurring in the first 100 d of the first lactation and subsequent lifelong risk of death and sale (and herd exit in general) of cows varied among farms. This implies that decisions on CM are farm-specific and may be due to different treatment protocols and culling strategies among the farms. All 5 farms were conventionally managed and fairly similar in terms of housing, level of milk production and herd size. While the findings from this study may apply to farms with similar characteristics, they may not be generalizable to other farms, particularly due to the observed farm variation. In management studies on health parameters on dairy farms, the farm effects are always large. These effects contain the differences among farms that are not explained by the models. Variability among farms is large, but it still remains relevant to study the similarities in biological effects among farms. These similar biological phenomena are what is explained by the regression models. Although the differences in pathogens' effects between farms might be regarded as a limitation to drawing generic conclusions, generic recommendations on disease prevention, treatment and culling are still useful. In all farms, early cases of CM in the life of a cow should be prevented and subsequently, specific recommendations with regard to treatment and culling by farm will provide further value.

High average daily cow milk production over the cow's productive lifetime was associated with a small increased risk of both death and sale. The hazard ratios for the pathogens did not change substantially

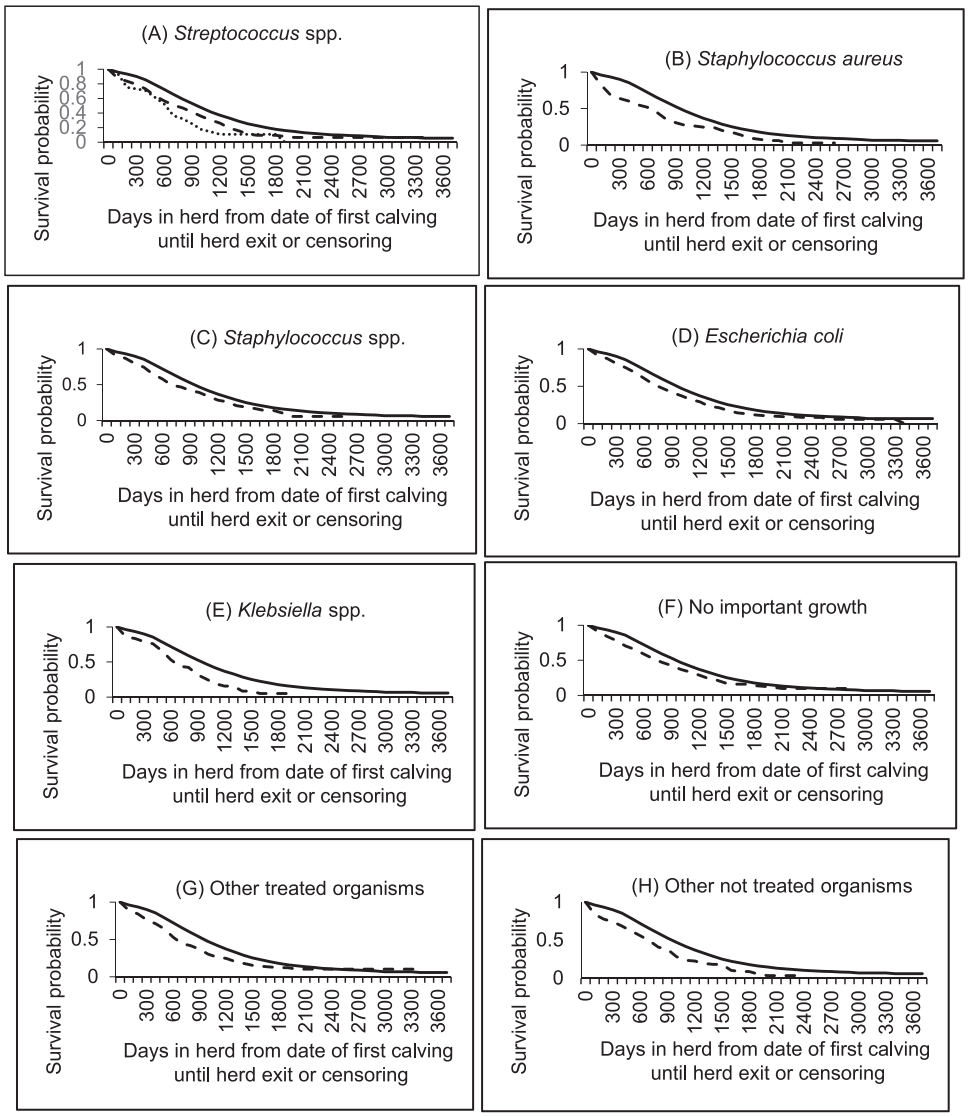



**Fig. 3.** Survival curves stratified by number of clinical mastitis (CM) cases (0: solid line; 1 or more: dashed line; 2 or more cases (*Streptococcus* spp. only): dotted line), by etiology, occurring in first 100 d of first lactation, in 24,831 cows (exited herd (n = 14,440) or still alive (n = 10,391)) in 5 New York State dairy herds, followed from 2004 until 2014. (A) *Streptococcus* spp. (including *Strep. dysgalactiae*, *Strep. uberis*, and other *Streptococcus* spp.), (B) *Staphylococcus aureus*, (C) *Staphylococcus* spp., (D) *Escherichia coli*, (E) *Klebsiella* spp., (F) CM cases with no important growth, (G) Other treated organisms (including *Corynebacterium bovis*, *Enterococcus*, *Pasteurella*, *Pseudomonas*, and other (unspecified) treated organisms), and (H) Other not treated organisms (including *Mycoplasma*, *Trueperella pyogenes*, and Yeast).

when milk production was omitted from the models (not shown). This implies that sale occurs because of the early life mastitis experiences regardless of the level of milk production of the individual cow. Similarly, death is related to the early life mastitis cases irrespective of the level of milk production. This independence of risk of removal due to mastitis with regard to milk production was present even though it has been shown previously that high producing cows tend to be more susceptible to mastitis (Hertl et al., 2014a). By including milk production in the models, we "corrected" the effects of CM on removal for milk production. We therefore suggest that cows are leaving the herd due to CM as a primary cause and not leaving the herd due to lower milk production as a consequence of CM.

In this study, overall, 10 % of cows died during the study period, ranging from 5.5 % to 14.3 % on individual farms. In addition, nearly half of the cows were sold during this time, from a low of 43.3 % to a high of 56.6 % on the 5 farms. One might expect a higher proportion of cows to have been sold, but this is based on the relatively long time it takes for a cohort of animals to complete their productive lifetimes on the farm. In these herds, cows began enrollment in the study in 2004, but only 6–7 years later would this first cohort be fully completed. That is only one-third of animals on the farm as only heifers enter the study. Then only from 2004 to 2007 would heifers entering the study be completely followed during their productive lifetime, but of the animals entering after 2007, a continuous increasing proportion would still be on the farm in 2014. As a result, about 60 % [50 (sale) + 10 (death)] of the enrolled animals' productive lifetimes were fully completed over the data period. This is intuitively low, but is actually quite realistic when taking these two effects (slow entry and over time an increasing proportion of censored cows) into account.

In the competing risks analyses, early occurring CM was associated more with sale than with death. With death as the event of interest (Table 3), only *E. coli* and CM with no growth appeared to be associated with death. The increased risk of death for *E. coli* was present throughout the time the cows were on the farm. In contrast, CM with no growth was associated with a lower probability of death, although this effect appears only after about 1500 d since date of first calving (Fig. 1). Signs of *E. coli* CM in early productive lifetime may thus warrant more vigilance. Cases with no growth, on the other hand, may be more likely to be mild and resolve quickly and without impact on future life expectancy.

With sale as the event of interest, *Streptococcus* spp., *Staph. aureus*, *Klebsiella* spp., cases due to other treated or not treated organisms, and cases with no growth were all associated with a higher rate of sale (Table 4). Fig. 2 indicates that this appeared to be the case throughout productive lifetime, as the survival curves for cows with these pathogens in the first 100 d of first lactation were consistently lower than the curves for cows without these pathogens in the first 100 d of first

**Table 6**
Hazard ratios, 95 % confidence intervals (CIs), and *P*-values for early-occurring[a] clinical mastitis pathogens' effects on length of productive lifetime, in 5 New York State Holstein dairy herds, from 2004—2014, from traditional Cox proportional hazards models. The event of interest was either death (model on left-hand side; 12,823 cows (2432 dead and 10,391 alive)) or sale (model on right-hand side; 22,399 cows (12,008 sold and 10,391 alive)). Cows still alive at end-of-study (4 February 2014) were censored. The data were stratified by herd.[b]

| | | Event: Death[c] | | | Event: Sale[d] | | |
|---|---|---|---|---|---|---|---|
| Pathogen | Number of cases in first 100 d of first lactation | Hazard Ratio | 95 % CI for Hazard Ratio | *P*-value | Hazard Ratio | 95 % CI for Hazard Ratio | *P*-value |
| *Streptococcus* spp. | 0 (reference level) | 1.0 | – | | 1.0 | – | |
| | 1 | 1.38 | 1.01, 1.89 | 0.0466 | 1.39 | 1.23, 1.58 | < 0.0001 |
| | 2 or more | 2.10 | 0.86, 5.09 | 0.1029 | 1.90 | 1.35, 2.67 | 0.0002 |
| *Staphylococcus aureus* | 0 | 1.0 | – | | 1.0 | – | |
| | 1 or more | 1.11 | 0.64, 1.94 | 0.7040 | 1.58 | 1.29, 1.93 | < 0.0001 |
| *Staphylococcus* spp. | 0 | 1.0 | – | | 1.0 | – | |
| | 1 or more | 0.99 | 0.64, 1.55 | 0.9709 | 0.93 | 0.77, 1.13 | 0.4794 |
| *Escherichia coli* | 0 | 1.0 | – | | 1.0 | – | |
| | 1 or more | 1.49 | 1.16, 1.93 | 0.0022 | 1.22 | 1.07, 1.38 | 0.0021 |
| *Klebsiella* spp. | 0 | 1.0 | – | | 1.0 | – | |
| | 1 or more | 1.63 | 0.84, 3.16 | 0.1465 | 1.65 | 1.28, 2.13 | 0.0001 |
| No growth | 0 | 1.0 | – | | 1.0 | – | |
| | 1 or more | 0.87 | 0.64, 1.18 | 0.3652 | 1.38 | 1.24, 1.54 | < 0.0001 |
| Other treated organisms | 0 | 1.0 | – | | 1.0 | – | |
| | 1 or more | 1.01 | 0.69, 1.46 | 0.9708 | 1.32 | 1.15, 1.52 | 0.0001 |
| Other not treated organisms | 0 | 1.0 | – | | 1.0 | – | |
| | 1 or more | 2.27 | 1.36, 3.77 | 0.0016 | 1.50 | 1.23, 1.83 | < 0.0001 |

[a] First 100 d of first lactation.
[b] Average daily milk production in a cow's productive lifetime was also included in the models (hazard ratio = 1.03 in both; $P < 0.0001$).
[c] No sold cows were included.
[d] No dead cows were included.

**Table 7**
Hazard ratios, 95 % confidence intervals (CIs), and *P*-values for early-occurring[a] clinical mastitis pathogens' effects on length of productive lifetime, in 24,831 cows in 5 New York State Holstein dairy herds, from 2004—2014, from traditional Cox proportional hazards models. The event of interest was either death (model on left-hand side; sold cows and cows still alive at end-of-study (4 February 2014) were censored) or sale (model on right-hand side; dead cows and cows still alive at end-of-study were censored). The data were stratified by herd.[b]

| | | Event: Death | | | Event: Sale | | |
|---|---|---|---|---|---|---|---|
| Pathogen | Number of cases in first 100 d of first lactation | Hazard Ratio | 95 % CI for Hazard Ratio | *P*-value | Hazard Ratio | 95 % CI for Hazard Ratio | *P*-value |
| *Streptococcus* spp. | 0 (reference level) | 1.0 | – | | 1.0 | – | |
| | 1 | 1.12 | 0.81, 1.54 | 0.4996 | 1.41 | 1.24, 1.59 | < 0.0001 |
| | 2 or more | 1.51 | 0.62, 3.70 | 0.3650 | 1.86 | 1.33, 2.61 | 0.0003 |
| *Staphylococcus aureus* | 0 | 1.0 | – | | 1.0 | – | |
| | 1 or more | 0.94 | 0.54, 1.64 | 0.8228 | 1.61 | 1.32, 1.97 | < 0.0001 |
| *Staphylococcus* spp. | 0 | 1.0 | – | | 1.0 | – | |
| | 1 or more | 0.97 | 0.62, 1.52 | 0.8820 | 0.96 | 0.79, 1.16 | 0.6484 |
| *Escherichia coli* | 0 | 1.0 | – | | 1.0 | – | |
| | 1 or more | 1.38 | 1.06, 1.78 | 0.0150 | 1.17 | 1.03, 1.32 | 0.0135 |
| *Klebsiella* spp. | 0 | 1.0 | – | | 1.0 | – | |
| | 1 or more | 1.12 | 0.57, 2.18 | 0.7490 | 1.65 | 1.28, 2.13 | 0.0001 |
| No growth | 0 | 1.0 | – | | 1.0 | – | |
| | 1 or more | 0.82 | 0.61, 1.11 | 0.2041 | 1.44 | 1.29, 1.60 | < 0.0001 |
| Other treated organisms | 0 | 1.0 | – | | 1.0 | – | |
| | 1 or more | 1.14 | 0.79, 1.65 | 0.4697 | 1.35 | 1.17, 1.55 | < 0.0001 |
| Other not treated organisms | 0 | 1.0 | – | | 1.0 | – | |
| | 1 or more | 1.48 | 0.90, 2.44 | 0.1222 | 1.52 | 1.25, 1.85 | < 0.0001 |

[a] First 100 d of first lactation.
[b] Average daily milk production in a cow's productive lifetime was also included in the models (hazard ratio = 1.02 in both; $P < 0.0001$).

lactation.

In the traditional survival analysis using the Cox proportional hazards model, with herd exit (due to either death or sale) (Table 5) as the outcome, *Streptococcus* spp., *Staph. aureus*, *E. coli*, *Klebsiella* spp., cases due to other treated or not treated organisms, and cases with no growth were all associated with herd exit. As in Figs. 1 and 2, the survival curves for cows with certain pathogens in the first 100 d of first lactation (Fig. 3) were consistently lower than the curves for cows without those pathogens in the first 100 d of first lactation. The hazard ratios in the traditional Cox proportional hazards model (Table 5) for the CM pathogens were higher than those in the competing risks model in which death was the event of interest (Table 3), but comparable to those in the competing risks model in which sale was the event of interest (Table 4). The reason for the more-similar estimates in the Cox and sale-as-event-of-interest models, compared with the Cox and death-as-event-of-interest models, may be because many more cows were sold (12,008) than died (2432).

Because sales outnumbered deaths by 5 to 1 in this dataset, the former exerted more influence on productive lifetime than the latter, as expected. This can be seen in Tables 3–7, in which pathogens were associated much more with sale than with death, regardless of how the events (death, sale) were handled in the analysis. Thus, with both analytical approaches (Cox proportional hazards models and proportional subdistribution hazards models with competing risks) producing

comparable hazard ratios, choice of method may depend on other considerations.

### 4.4. Study limitations

This study had several limitations. First, with competing events, no one analytical approach may be the perfect modeling procedure. The subdistribution method may not appear rational, as cows experiencing a competing event are still in the risk set for the event of interest. It is appropriate, however, in estimating cumulative incidence functions. Second, there was variability in pathogens' occurrence among the farms. This may be truly the case, or it may reflect data error due to differences in detection, recording, or in treating/not treating of CM cases. Such biases could result in under- or over-estimates of the association between pathogen-specific CM and herd exit. The study farms, however, were selected in large part for their good recordkeeping and management. The variability implies that decisions on CM are farm-specific and may differ by treatment protocol and culling strategy. Protocols were similar among farms, however, so other factors may be at play. Third, related to this, misclassification in coding cows as "sold" vs. "died" may have occurred. It is also possible that the definition of "death" (vs. "sold") changed over the 10-yr study period, or differed between farms. Thus, misclassification bias may exist between farms as a whole, or between cows within a farm. The latter two points (pathogen variability and misclassification bias) indicate that the findings from this study may not apply to farms with different characteristics.

The earliest observations in our dataset are now approaching 20 years old. Over that time, some factors, including various management practices, have changed in the dairy industry, and new technology has developed. Use of sexed semen has gained ground, due to its economic benefits, although the fertility of sexed semen is lower than that of unsexed semen (Williams, 2021). Genetic testing of heifers, through e.g., producing animals that reach puberty sooner and have higher pregnancy rates (Meier et al., 2021) may change culling decisions. Use of genetic information in future studies could help in selection of mastitis resistance traits (Kaniyamattam et al., 2020), further potentially changing both culling decisions and mortality. This would have a number of benefits, including increasing productive lifetime, reducing antimicrobial use in CM cases not necessitating use, thereby encouraging antimicrobial stewardship, and improving herd health and performance overall. These measures would thus further enable optimal cow and herd management, promoting sustainability. In addition, certain regulations on somatic cell counts have changed (APHIS, 2021), which may also influence culling decisions. Nevertheless, our dataset is an excellent resource to illustrate the different methodological approaches that can be used to address the problem of competing events (the purpose of this study) and its age is not relevant in this context.

## 5. Conclusions

This study used proportional hazards models with competing risks to account for death as the event of interest and sale as the competing event in one model, and alternatively sale as the event of interest and death as the competing event in another. We also compared results from this analytical approach with the traditional survival analysis utilizing the Cox proportional hazards model, with herd exit overall (i.e., due to either death or sale) as the event. The modified method accounting for competing risks may be more appropriate in the context of competing events (death, sale) than standard survival analysis, resulting in less biased estimates. The estimates from our Cox model were higher than those in the competing risks model in which death was the event of interest, but similar to those in the competing risks model in which sale was the event of interest. Also, differences between causative pathogens were observed. For example, *E. coli* was mostly associated with an increased death rate while *Staph. aureus* was only associated with an increased rate of sale. The findings from the current study may help to manage cows that contract CM of different etiologies in their early productive lifetime. Nevertheless, given the differences among farms in this study, how a farmer handles CM in relation to herd removal appears to be farm-specific. In any case, early lactation CM in first-lactation cows was an important factor explaining an increased risk of sale from the herd. Hence, recommendations with regard to mastitis control in first-lactation cows via sanitation, milking practices and other mastitis prevention practices are of great value, not only with regard to immediate CM costs but also with regard to an increased lifelong risk of removal from the herd.

## Acknowledgements

The USDA (CSREES) Award No. 2010-65119-20478 and Cornell University Hatch Project NYC-121856 provided funding for this study. The authors thank owners and personnel from the 5 dairies, and the personnel of the Ithaca, Canton, and Geneseo Regional Laboratories, Quality Milk Production Services, for their valuable cooperation. The authors state no conflicts of interest.

## References

Abdel-Qadir, H., Fang, J., Lee, D.S., Tu, J.V., Amir, E., Austin, P.C., Anderson, G.M., 2018. Importance of considering competing risks in time-to-event analyses. Application to stroke risk in a retrospective cohort study of elderly patients with atrial fibrillation. Circ.: Cardiovasc. Qual. Outcomes 11 (7). https://doi.org/10.1161/CIRCOUTCOMES.118.004580, 11 pages.

Adamczyk, K., Makulska, J., Jagusiak, W., Węglarz, A., 2017. Associations between strain, herd size, age at first calving, culling reason and lifetime performance characteristics in Holstein-Friesian cows. Animal 11 (2), 327–334. https://doi.org/10.1017/S1751731116001348.

Allison, P., 2018. For Causal Analysis of Competing Risks, Don't Use Fine & Gray's Subdistribution Method. ⟨https://statisticalhorizons.com/for-causal-analysis-of-competing-risks⟩ (Accessed 15 November 2021).

SAS Institute, 2017. SAS Help and Documentation. SAS version 9.4. SAS Institute Inc, Cary, NC.

Ansari-Lari, M., Mohebbi-Fani, M., Rowshan-Ghasrodashti, A., 2012. Causes of culling in dairy cows and its relation to age at culling and interval from calving in Shiraz, Southern Iran. Vet. Res. Forum 3 (4), 233–237.

APHIS Veterinary Services, Center for Epidemiology and Animal Health., 2021. Determining U.S. milk quality using bulk-tank somatic cell counts, 2019. (June 2021). ⟨https://www.aphis.usda.gov/animal_health/nahms/dairy/downloads/dairy_monitoring/btscc_2019infosheet.pdf⟩ (Accessed 18 April 2022).

Armengol, R., Fraile, L., 2018. Descriptive study for culling and mortality in five high-producing Spanish dairy cattle farms (2006-2016). Acta Vet. Scand. 60 45 (11 pages). https://doi.org/10.1186/s13028-018-0399-z.

Austin, P.C., Lee, D.S., Fine, J.P., 2016. Introduction to the analysis of survival data in the presence of competing risks. Circulation 133, 601–609. https://doi.org/10.1161/CIRCULATIONAHA.115.017719.

Barkema, H.W., Schukken, Y.H., Lam, T.J., Beiboer, M.I., Wilmink, H., Benedictus, G., Brand, A., 1998. Incidence of clinical mastitis in dairy herds grouped in three categories by bulk milk somatic cell counts. J. Dairy Sci. 81, 411–419. https://doi.org/10.3168/jds.S0022-0302(98)75591-2.

Beaudeau, F., Ducrocq, V., Fourichon, C., Seegers, H., 1995. Effect of disease on length of productive life of French Holstein dairy cows assessed by survival analysis. J. Dairy Sci. 78, 103–117. https://doi.org/10.3168/jds.S0022-0302(95)76621-8.

Beaudeau, F., Seegers, H., Ducrocq, V., Fourichon, C., Bareille, N., 2000. Effect of health disorders on culling in dairy cows: a review and a critical discussion. Ann. Zootech. 49, 293–311. https://doi.org/10.1051/animres:2000102.

Cha, E., Hertl, J.A., Schukken, Y.H., Tauer, L.W., Welcome, F.L., Gröhn, Y.T., 2013. The effect of repeated episodes of bacteria-specific clinical mastitis on mortality and culling in Holstein dairy cows. J. Dairy Sci. 96, 4993–5007. https://doi.org/10.3168/jds.2012-6232.

Cha, E., Kristensen, A.R., Hertl, J.A., Schukken, Y.H., Tauer, L.W., Welcome, F.L., Gröhn, Y.T., 2014. Optimal insemination and replacement decisions to minimize the cost of pathogen-specific clinical mastitis in dairy cows. J. Dairy Sci. 97, 2101–2117. https://doi.org/10.3168/jds.2013-7067.

Cox, D., 1972. Regression models and life tables (with discussion). J. Roy. Stat. Soc. – Ser. B 34, 187–220. https://doi.org/10.1111/j.2517-6161.1972.tb00899.x.

De Oliveira, E.B., Cunha, F., Daetz, R., Figueiredo, C.C., Chebel, R.C., Santos, J.E., Risco, C.A., Jeong, K.C., Machado, V.S., Galvão, K.N., 2020. Using chitosan microparticles to treat metritis in lactating dairy cows. J. Dairy Sci. 103, 7377–7391. https://doi.org/10.3168/jds.2019-18028.

De Sevilla, X.F., Fàbrega, E., Tibau, J., Casellas, J., 2009. Competing risk analyses of longevity in Duroc sows with a special emphasis on leg conformation. Animal 3, 446–453. https://doi.org/10.1017/S1751731108003583.

DeVries, A., 2020. Symposium review: Why revisit dairy cattle productive lifespan? J. Dairy Sci. 103, 3838–3845. https://doi.org/10.3168/jds.2019-17361.

Dürr, J.W., Monardes, H.G., Cue, R.I., 1997. Competing risks analysis of reasons for disposal in Quebec dairy herds. Dept. of Animal Science, McGill University. 7 pages. ⟨https://escholarship.mcgill.ca/concern/papers/4×51hp81k⟩ (Accessed 10 June 2021).

Feakins, B.G., McFadden, E.C., Farmer, A.J., Stevens, R.J., 2018. Standard and competing risk analysis of the effect of albuminuria on cardiovascular and cancer mortality in patients with type 2 diabetes mellitus. Diagn. Progn. Res. 2 (13) https://doi.org/10.1186/s41512-018-0035-4, 9 pages.

Fetrow, J., Nordlund, K.V., Norman, H.D., 2006. Invited review: culling: nomenclature, definitions, and recommendations. J. Dairy Sci. 89, 1896–1905. https://doi.org/10.3168/jds.S0022-0302(06)72257-3.

Fine, J.P., Gray, R.J., 1999. A proportional hazards model for the subdistribution of a competing risk. J. Am. Stat. Assoc. 94, 496–509. https://doi.org/10.2307/2670170.

Freebern, E., Santos, D.J.A., Fang, L., Jiang, J., Parker Gaddis, K.L., Liu, G.E., VanRaden, P.M., Maltecca, C., Cole, J.B., Ma, L., 2020. GWAS and fine-mapping of livability and six disease traits in Holstein cattle. BMC Genom. 21 (41) https://doi.org/10.1186/s12864-020-6461-z, 11 pages.

Gondara, L., 2015. Competing risk survival analysis using SAS®. support.sas.com/resources/papers/proceedings15/1424–2015.pdf (accessed 8 June 2021).

Gröhn, Y.T., Eicker, S.W., Ducrocq, V., Hertl, J.A., 1998. Effect of diseases on the culling of Holstein dairy cows in New York State. J. Dairy Sci. 81, 966–978. https://doi.org/10.3168/jds.S0022-0302(98)75657-7.

Gröhn, Y.T., Rajala-Schultz, P.J., Allore, H.G., DeLorenzo, M.A., Hertl, J.A., Galligan, D. T., 2003. Optimizing replacement of dairy cows: modeling the effects of diseases. Prev. Vet. Med. 61, 27–43. https://doi.org/10.1016/s0167-5877(03)00158-2.

Gröhn, Y.T., Wilson, D.J., González, R.N., Hertl, J.A., Schulte, H., Bennett, G., Schukken, Y.H., 2004. Effect of pathogen-specific clinical mastitis on milk yield in dairy cows. J. Dairy Sci. 87, 3358–3374. https://doi.org/10.3168/jds.S0022-0302(04)73472-4.

Gröhn, Y.T., González, R.N., Wilson, D.J., Hertl, J.A., Bennett, G., Schulte, H., Schukken, Y.H., 2005. Effect of pathogen-specific clinical mastitis on herd life in two New York State dairy herds. Prev. Vet. Med. 71, 105–125. https://doi.org/10.1016/j.prevetmed.2005.06.002.

Gussmann, M., Denwood, M., Kirkeby, C., Farre, M., Halasa, T., 2019. Associations between udder health and culling in dairy cows. Prev. Vet. Med. 171 https://doi.org/10.1016/J.PREVETMED.2019.104751. Article 104751.

Hagiwara, S., Mori, K., Nagahata, H., 2016. Predictors of fatal outcomes resulting from acute *Escherichia coli* mastitis in dairy cows. J. Vet. Med. Sci. 78, 905–908. https://doi.org/10.1292/jvms.15-0400.

Haine, D., Delgado, H., Cue, R., Sewalem, A., Wade, K., Lacroix, R., Lefebvre, D., Arsenault, J., Bouchard, E., Dubuc, J., 2017. Marginal structural Cox model to estimate the causal effect of clinical mastitis on Québec dairy cow culling risk. Prev. Vet. Med. 147, 124–131. https://doi.org/10.1016/j.prevetmed.2017.08.017.

Hertl, J.A., Schukken, Y.H., Welcome, F.L., Tauer, L.W., Gröhn, Y.T., 2014a. Pathogen-specific effects on milk yield in repeated clinical mastitis episodes in Holstein dairy cows. J. Dairy Sci. 97, 1465–1480. https://doi.org/10.3168/jds.2013-7266.

Hertl, J.A., Schukken, Y.H., Welcome, F.L., Tauer, L.W., Gröhn, Y.T., 2014b. Effects of pathogen-specific clinical mastitis on probability of conception in Holstein dairy cows. J. Dairy Sci. 97, 6942–6954. https://doi.org/10.3168/jds.2014-8203.

Hertl, J.A., Schukken, Y.H., Tauer, L.W., Welcome, F.L., Gröhn, Y.T., 2018. Does clinical mastitis in the first 100 days of lactation 1 predict increased mastitis occurrence and shorter herd life in dairy cows? J. Dairy Sci. 101, 2309–2323. https://doi.org/10.3168/jds.2017-12615.

International Dairy Federation, 2011. Suggested interpretation of mastitis terminology. Bulletin of the IDF: 448/2011. International Dairy Federation, Brussels, Belgium.

Kalbfleish, J.D., Prentice, R.L., 2002. The Statistical Analysis of Failure Time Data, Second ed. John Wiley and Sons, Inc, Hoboken, NJ, pp. 247–265. https://doi.org/10.1002/9781118032985.

Kaniyamattam, K., De Vries, A., Tauer, L.W., Gröhn, Y.T., 2020. Economics of reducing antibiotic usage for clinical mastitis and metritis through genomic selection. J. Dairy Sci. 103, 473–491. https://doi.org/10.3168/jds.2018-15817.

Maher, P., Good, M., More, S.J., 2008. Trends in cow numbers and culling rate in the Irish cattle population, 2003 to 2006. Ir. Vet. J. 61 (7), 455–463. https://doi.org/10.1186/2046-0481-61-7-455.

Maia, R.P., Ask, B., Madsen, P., Pedersen, J., Labouriau, R., 2014. Genetic determination of mortality rate in Danish dairy cows: A multivariate competing risk analysis based on the number of survived lactations. J. Dairy Sci. 97, 1753–1761. https://doi.org/10.3168/jds.2013-6959.

McConnel, C.S., McNeil, A.A., Hadrich, J.C., Lombard, J.E., Heller, J., Garry, F.B., 2018. A comparison of a novel time-based summary measure of dairy cow health against cumulative disease frequency. Ir. Vet. J. 71 (7) https://doi.org/10.1186/s13620-018-0119-z, 14 pages.

Meier, S., McNaughton, L.R., Handcock, R., Amer, P.R., Beatson, P.R., Bryant, J.R., Dodds, K.G., Spelman, R., Roche, J.R., Burke, C.R., 2021. Heifers with positive genetic merit for fertility traits reach puberty earlier and have a greater pregnancy rate than heifers with negative genetic merit for fertility traits. J. Dairy Sci. 104, 3707–3721. https://doi.org/10.3168/jds.2020-19155.

Moussavi, A.H., Mesgaran, M.D., Gilbert, R.O., 2012. Effect of mastitis during the first lactation on production and reproduction performance of Holstein cows. Trop. Anim. Health Prod. 44, 1567–1573. https://doi.org/10.1007/s11250-012-0107-3.

Olechnowicz, J., Jaśkowski, J.M., 2011. Reasons for culling, culling due to lameness, and economic losses in dairy cows. Med. Weter. 67 (9), 618–621.

Pattamanont, P., Galvão, K.N., Marcondes, M.I., Clay, J.S., De Vries, A., 2021. Associations between dry period length and time to culling and pregnancy in the subsequent lactation. J. Dairy Sci. 104, 8885–8900. https://doi.org/10.3168/jds.2021-20119.

Pritchard, T., Coffey, M., Mrode, R., Wall, E., 2013. Genetic parameters for production, health, fertility and longevity traits in dairy cows. Animal 7 (1), 34–46. https://doi.org/10.1017/S1751731112001401.

Puerto, M.A., Shepley, E., Cue, R.I., Warner, D., Dubuc, J., Vasseur, E., 2021. The hidden cost of disease: I. Impact of the first incidence of mastitis on production and economic indicators of primiparous dairy cows. J. Dairy Sci. 104 (7) https://doi.org/10.3168/jds.2020-19584.

Reksen, O., Sølverød, L., Østerås, O., 2007. Relationships between milk culture results and milk yield in Norwegian dairy cattle. J. Dairy Sci. 90, 4670–4678. https://doi.org/10.3168/jds.2006-900.

Santos, J.E.P., Cerri, R.L.A., Balloa, M.A., Higginbotham, G.E., Kirk, J.H., 2004. Effect of timing of first clinical mastitis occurrence on lactational and reproductive performance of Holstein dairy cows. Anim. Reprod. Sci. 80, 31–45. https://doi.org/10.1016/S0378-4320(03)00133-7.

Silva, N., Costa, G.M., 2001. An outbreak of acute bovine mastitis caused by Klebsiella pneumoniae in a dairy herd. Arq. Bras. Med. Vet. Zootec. 53, 1–5. https://doi.org/10.1590/S0102-09352001000400001.

Southey, B., Rodriguez-Zas, S., Leymaster, K., 2004. Competing risks analysis of lamb mortality in a terminal sire composite population. J. Anim. Sci. 82, 2892–2899. https://doi.org/10.2527/2004.82102892x.

Vakkamäki, J., Taponen, S., Heikkilä, A.-M., Pyörälä, S., 2017. Bacteriological etiology and treatment of mastitis in Finnish dairy herds. Acta Vet. Scand. 59 (33) https://doi.org/10.1186/s13028-017-0301-4, 9 pages.

Williams, C., 2021. Using sexed semen and genetic technologies to improve dairy and beef herds. ⟨https://businesswales.gov.wales/farmingconnect/news-and-events/technical-articles/using-sexed-semen-and-genetic-technologies-improve-dairy-and-beef-herds⟩ (Accessed 18 April 2022).