A study of the dynamics of digital dermatitis in 742 lactating dairy cows

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Summary

Digital dermatitis (DD) is a contagious disease of cattle affecting the skin of the claw. The disease presents with a range of severities and can be associated with lameness. Information about the disease dynamics of DD is scarce. Parity and lactation stage have been identified as risk factors for DD and studies have also indicated that not all cows are equal regarding their risk of recurrent disease and prospects for cure from DD. The aim of this study was to investigate host heterogeneity to DD and to identify disease patterns of DD and factors associated with the development and resolution of lesions. In three commercial dairy herds, 742 lactating cows were observed for DD lesions weekly for 11 or 12 weeks. The effects of parity, lactation stage and duration of preceding episode on the hazard of transitions between healthy and lesion states were analysed using a multilevel multistate discrete-time model. One or more DD lesions were observed in 460 cows and lesions were observed in 2426 out of 10585 observations. In total, 1755 uncensored episodes with DD lesions were observed. Early lactation was associated with a reduced risk of developing lesions compared with mid and late lactation. Lesions that developed in late lactation had a greater likelihood of resolution compared with lesions that developed during early lactation. There was a reduced risk of lesions developing in parity 3 compared with parity 1 cows, but an increased risk of lesions developing in parity 2 compared with parity 1 cows. In the present study, the mean duration of uncensored DD episodes was 1.7 weeks indicating that the duration of the majority of DD lesions might be shorter than the 42 days reported previously. The transitions between disease states suggest that DD is a dynamic disease, and that the early stage lesions are more transient than expected from previous studies. We conclude that studies with shorter observation intervals than one week are needed to fully understand and describe the individual and group dynamics of DD.

Key words: Digital dermatitis, Dairy cow, Multistate multilevel discrete-time model, Disease dynamics

Introduction

Digital dermatitis (DD) is a contagious disease of cows affecting the skin of the claw. Lesions are painful and can be a cause of lameness. DD lesions are present in 70-95% of dairy herds in the USA and Denmark (Capion et al., 2008; Cramer et al., 2008) with a within herd prevalence of 20-30% in Europe and the USA (Holzhauer et al., 2006; Capion et al., 2008; Cramer et al., 2008; Barker et al., 2009). Diseases associated with lameness in dairy cows can reduce milk yield and have a negative economic impact (Enting et al., 1997; Green et al., 2002; Bicalho et al., 2008; Ettema et al., 2010). Although DD is sometimes associated with reduced yield (de Jesus Argaez-Rodriguez et al., 1997) this is not always the case (Amory et al., 2008; Tadich et al., 2010). The financial costs due to single cases of DD are not as high as those for sole ulcer or white line disease (Ettema et al., 2007), but because of the high prevalence of DD, there is a high cost in terms of time spent treating DD lesions (Bruijnis et al., 2010) and cow welfare is compromised.

Digital dermatitis appears to be caused by several species of bacteria and certain *Treponema* species play a crucial role (Yano et al., 2010; Klitgaard et al., 2008; Demirkan et al., 1998, Döpfer et al., 1997). An increased risk of DD has been associated with the early stages of lactation and first and second parity cows (Somers et al., 2005a; Holzhauer et al., 2006; Barker et al., 2009). Holzhauer et al. (2008a) reported that cows in their first or second parity were at greater risk of persistent or recurrent disease compared with cows in parity three or more. Poor hygiene in the cows' environment has been associated with a higher risk of disease (Barker et al., 2009; Somers et al., 2005a; Rodriguez-Lainz et al., 1999; Nowrouzian & Radgohar, 2011).

There is a range of stages of DD lesions which are reflected in different DD scoring systems (Döpfer et al., 1997; Manske et al., 2002). Döpfer et al. (1997) described four disease classes based on gross as well as histological evaluation: early lesions, classical ulcerations, healing lesions and lesions of suspected DD. Manske et al. (2002) described five disease stages on a nominal scale from 1-5 based on a gross examination of lesions. Scores 1 and 2 are early lesions with an intact epidermis, score 3 is an ulcerative lesion with no signs of healing and scores 4 and 5 are late lesions in the process of healing.

It has been suggested that cows could be grouped according to their 'DD history' by having no lesions, single lesions or recurring lesions (Dopfer et al., 2004; Holzhauer et al., 2008a) thereby indicating that not all individuals are equal regarding their risk of recurrent infections and prospect of cure from DD. In many studies, DD lesions are considered to be persistent. Nielsen et al. (2009) reported durations of clinical, topically treated DD lesions of approximately 40 days and other studies have reported that ulcerative lesions persist for months (Dopfer et al., 1997; Somers et al., 2005b). Nevertheless, Holzhauer et al., (2008b) reported that weekly transitions between disease stages were frequent, occurring in 39-67% of cases. This indicates that studies with frequent observations are needed to describe disease dynamics in details.

Recent advances in analytical tools include multistate models where the transition between states can be modelled jointly allowing for correlations between states to allow for unobserved host heterogeneity and testing whether the effects of predictor variables are state specific. Multilevel multistate discrete-time models are composed of simultaneous equations for transitions between diseased and healthy states, where each equation defines a discrete-time hazard. It was first described by Steele et al. (2004). The discrete-time approach is used when observations are made at intervals and it is therefore natural to specify a model that assumes measurements in discrete time. Standard methods for analysing discrete response data apply to this type of data and existing estimation procedures can be used to fit even complex event-history models (Steele et al., 2005). When events can occur more than once to an individual, unobserved individual-specific risk factors can be present affecting the occurrence of each event and so the occurrence and/or durations between events within same individual might be correlated. This possible dependence between event times within individuals can be investigated with a hierarchical structure, with events nested within individuals and allowing for correlation between random effects for different events.

The hypothesis of the present study was that cows are heterogeneous in their probability of DD disease occurrence, duration and resolution. The aim of this study was to investigate host heterogeneity to DD and to identify disease patterns of DD and factors associated with the development and resolution of lesions that might direct future research or inform advisors and farmers.

Materials and methods

Source of data

The data were sourced from three commercial Danish dairy herds that were among eight farms in a clinical trial conducted to evaluate the effects of automatic hoof washing on prevention and cure of DD. In all three herds, the cows were housed in loose housing systems with mattress or mat bedded cubicles. Herds A and B had slatted floors, whereas herd C had a solid concrete floor; all floors were scraped by automatic scrapers. None of herds used pasture grazing and none of the cows had access to outdoor areas. All three had a milking carrousel, which provided good conditions for scoring DD lesions during milking. Information about individual cows was obtained from the Danish Cattle Database. The dominant breed in all three herds was Danish Holstein (DH).

All three herds were in a clinical trial and as a consequence each herd had an automatic hoof washing machine that washed the left feet of each lactating cow after every milking; the right feet were left unwashed. For the weekly examinations, conducted in the present study, both hind legs were washed manually with a water hose in order to evaluate the skin in the heel region for DD lesions. During the study period, DD lesions could be individually treated by the owners using their normal routine (there was no specific protocol) typically bandages containing salicylic acid. All cows' feet in the three herds were examined in a hoof trimming chute shortly before the study started and once during the study period and their feet were trimmed if necessary.

Observations

Observations of DD lesions were made during milking as described by Thomsen et al. (2008). DD lesions were recorded on 12 occasions in two herds and on 11 occasions in one herd with a mean interval of 6.9 days (SD = 1.06; range 5 - 9) between observations. The DD lesions were scored using an ordinal scale described by Manske et al. (2002) (Table 2). Only lesions in the skin in the heel region of the hind feet were scored and if more than one lesion was present the most predominant lesion on a foot was recorded. Observations were done by BHN, PTT or a trained research technician from Aarhus University. All observers were highly trained and experienced in the use of the scoring system presented by Manske et al. (2002). Before starting the observations, the three observers were calibrated by looking at pictures of DD lesions and discussing the DD scoring system in order to obtain a high degree of agreement.

Statistical analysis

Missing observations at the beginning and end of the observation period were excluded from the analysis and when data were missing from the middle of the observation period (for example when a cow was away during the dry period) only the longest uninterrupted sequence of observations from each individual was used. Only data from cows with more than one observation were kept. Frequency distributions and measures of central tendency and dispersion were done in SAS version 9.1 (SAS Inst., Inc., Cary; NC, USA). The number of cows and feet that had, or developed, DD and the cases of DD by lesion score for each week were calculated. Occurrence of DD lesions was defined as a change from no lesion to a lesion of any lesion score from one observation to next. Likewise, resolution of DD lesions was defined as change from any lesion score to no lesion at the next observation. The number of lesion occurrences and resolutions as well as transitions between disease states was explored. The incident lesions per weekly observation were calculated with the denominator excluding those feet with a lesion at the previous observation. The mean number of incident lesions per affected cow and the mean duration of lesion episodes were calculated.

A multivariable multistate discrete time model was run in MLwiN 2.18 (Rasbash et al., 2004). For the multistate model two states were defined 0 = healthy (no DD lesion), 1 = diseased (DD score > 0). Data were censored at the end of the study. An episode was a continuous period of time (measured in discrete-time intervals) one foot spent in one state until a transition or censoring occurred. For each episode *j* for foot *k* for cow *l* the duration spent in state *i* was categorised into discrete-time intervals of week where $t_{ij} = 1, 2, \ldots$, n with *n* being the maximum duration of an episode and an outcome event at the end of the discrete-time interval, *y*, depicting whether a transition occurred (*y* = 0 if no change of state; *y* = 1 if change from healthy to diseased (= occurrence) or from diseased to healthy (= resolution)). Each leg could experience multiple transitions between states over time and thus have multiple episodes.

Model setup

If we denote by $h^{(ri)}_{tijkl}$ the hazard of transition from origin state *i* to transition state r_i during discrete-time interval *t* of episode *j* for foot *k* for cow *l*, and $h^{(0)}_{tijkl}$ denotes the hazard of no transition, a multilevel, multistate discrete-time model may be written as

$$\log (h^{(ri)}_{tijkl} / h^{(0)}_{tijkl}) =$$

$$\beta^{(ri)}_0 + \beta^{(ri)}_i z^{(ri)}_{tijkl} + \beta^{(ri)}_i DIM^{(ri)}_{tijkl} + \beta^{(ri)}_i Parity^{(ri)}_{tijkl} + \beta^{(ri)}_i Leg^{(ri)}_{tijkl} + \mu^{(ri)}_{il}$$

$$r_i = 0, 1; \qquad i = 0, 1.$$

where $\beta^{(ri)}_0$ is the state-specific intercept, $\beta^{(ri)}_i z^{(ri)}_{tijkl}$ represents the effect of duration which in this case takes a piece-wise constant step function of time with duration intervals of 1, 2, 3-6 and 7+ weeks. The covariates days in milk (DIM,) parity and foot are defined at cow-level. Unobserved cow-specific factors that vary by state are represented by the random effects $\mu^{(ri)}_{il}$. Random effects are assumed to follow a multivariate Normal distribution with covariance structure Ω_μ and non zero correlation between random effects.

Covariates

The model included the following fixed effects: Days in milk (DIM) (categorical; 1 = 0-90 DIM / 2 = 91-180 DIM / 3 = >180 DIM), parity (categorical; 1 / 2 / ≥3), herd (categorical; A / B / C) and foot (binary; left (washed) / right (unwashed)). DIM was fixed at the first discrete time interval of an episode.

The parameter estimates from the model was fitted with Monte Carlo Markov chain (MCMC) estimation for 500,000 iterations with a burn in of 5000. Chain mixing and stability were evaluated visually. The model was rerun excluding left feet.

Results

Descriptive results

The characteristics of the three herds regarding size, milk production, number of observations from each herd, distribution of cows in parity groups and lactation stages (DIM) and prevalence of DD lesions are presented in Table 1. The prevalence and incidence of lesions varied by farm.

In total, 14051 observations were made on 760 cows. Of these, 3466 (25%) observations (18 – 31% per herd) were excluded for reasons stated in the methods. The final data set contained 5300 observations from the left leg (739 cows) and 5285 from the right leg (738 cows); in total there were 10585 observations on 742 cows. The mean number of observations from the left leg was 7.2 (SD: 3.2) per cow and from the right leg 7.2 (SD: 3.3) per cow. There were 282/742 (38%) cows which had no lesions during the study period. DD lesions were observed on 460/742 (62%) cows on at least one occasion. At the recordings, 407 cows presented with a lesion on one foot only and 246 cows had lesions on both feet on at least one occasion. Furthermore, 250 cows had a DD lesion present at their first observation and 390 incident cases (new cases in feet at risk) were observed, corresponding to each affected cow having a median of 2 (inter quartile range (IQR) = 1-3) occurrences of lesions.

Only a few cases of lesion scores 1 or 2 were observed; the majority were scores 3 – 5 (Table 2). The majority of healthy episodes remained healthy at the next observation (Table 3). Transitions between states occurred in both directions. The most common transition in both feet was from healthy to DD lesion score 5 (60% and 53% of transitions on left and right foot respectively). In the left leg, resolution were seen in 50% of score 2, 22% of score 3, 26% of score 4 and 50% of score 5 lesions. A similar pattern was seen in the right foot (Table 3). Approximately 50% of score 3 lesions persisted at score 3, whilst approximately 30% of score 4 and 5 lesions remained at the same lesion score from one observation to the next.

There were 1755 uncensored episodes: 848 were on the left foot (440 occurrences + 408 resolutions) and 907 were on the right foot (483 occurrences + 424 resolutions) (Table 4). The number of transitions by explanatory variables is presented in Table 5. Lesions developed in 11% (923/8159) of healthy episodes and resolution was observed in 34% of diseased episodes (832/2426) (Table 4). There was no significant difference in the number or direction of transitions between left and right foot (Table 4).

The prevalence of incident cases over time stratified by herd is illustrated in Figure 1. The mean prevalence of incident lesions per observation was 12.6 / 100 feet (SD: 9.8; Median: 7.5; IQR = 6.0-19.2). Of the censored episodes, 1363 had no lesion and 730 had lesions at the time of censoring. There were 64% (535/832) of recoveries in the first time interval, 46% (138/297) of those still affected recovered in the second time interval and 95% (151/159) of those still affected recovered during the third to sixth time interval. The pattern of resolutions was similar in each foot (results not shown). The mean duration of uncensored DD episodes was 1.7 weeks (SD = 1.2; median = 1; IQR = 1-2), 54% (603/1118) of episodes had a duration of 1 week (Table 6).

Multilevel multistate model

Results from the parameter estimation are presented as odds ratios (OR) with 95% credibility intervals (CI) in Table 7.

Second parity cows were more likely to develop lesions than first parity cows (OR = 1.28; CI = 1.06-1.53), whereas cows of parity 3 or more were less likely to develop lesions (OR = 0.80; CI = 0.64-0.99). Cows in early lactation were less likely to develop a lesion than cows in mid (OR = 1.37; CI 1.10-1.71) or late (OR = 1.27; CI = 1.05-1.53) lactation, whereas resolution was more likely when lesions developed in late lactation (OR = 1.27; CI = 1.00-1.60) compared with early lactation. The duration of an episode had a significant effect on the risk of occurrence and resolution. The longer a period without a lesion the less likely a transition to a lesion was to occur. Also, resolution was more likely the shorter the lesion episode. Although not significant, the probability of resolution tended to be higher in the left, washed foot than in the right, unwashed foot (OR=1.18; 95% CI: 0.97-1.43).

When fitting a basic model only including duration effects (estimates not shown), the estimated random effects (footnote to Table 7) showed evidence of unobserved heterogeneity between cows in their hazard of particularly lesion occurrence (p-value < 0.05; confidence interval (CI) = 0.25-0.75), but also resolution (p-value < 0.05; CI = 0.03-0.17). After including covariates there was no evidence of any unexplained random variability between cows in any states. There was non significant correlation between random effects. The model converged visually with stable chain mixing. The model with right feet only gave the same results (direction and magnitude) except that confidence intervals were wider because there was less power in the study (data not shown).

Discussion

The objective of the present study was to investigate the occurrence and patterns of DD in cattle observed each week for 12 weeks and to investigate host heterogeneity to DD. This study is the first study exploring the dynamics between diseases states in cattle observed each week using a multilevel multistate discrete-time model; this model has been recently used to investigate the factors associated with transition between lameness states in sheep (Kaler et al., 2010).

Existing studies on DD describe DD as a prevalent and rather persisting disease (Dopfer et al., 1997; Capion et al., 2008; Holzhauer et al., 2006; Nielsen et al., 2009). The majority of studies have observed DD on a monthly basis, which seems plausible given the assumption that a lesion lasts approximately 50 days. However, as shown by Holzhauer et al. (2008b) weekly transitions between disease stages are common and based on this, we decided that weekly observations would be appropriate to elucidate patterns of transition between disease states. Nevertheless, few observations of early disease stages (scores 1 and 2) were made in the present study, indicating that these transitions occurred very rapidly. In addition, the majority of transitions from disease to healthy occurred within two weeks. The rapid resolution of DD lesions was unexpected given previous research. By observing more than once a week, more information might have been gained on these rapid transitions. Therefore, results from this study suggest that it would be beneficial to decrease observation intervals in future studies aiming at learning more about changes in DD disease states. However, as lesions can only be evaluated after washing more frequent observation also means more frequent washing. This could possibly have an effect on the prevalence (by reducing persistence) of lesions. It might be that one month intervals (as used in many previous studies) are sufficiently long to fail to observe resolution and reoccurrence with a second episode of disease (those cows affected in the current study have a median of 2 occurrences of disease in 12 weeks, so monthly recording might have indicated persistent disease of 8 or 12 weeks). A larger study would have been useful because even with >700 cows with weekly observations there were insufficient data to analyse transitions between different lesion scores of DD lesions in the multistate model.

The nearest similar study to the current paper was by Holzhauer et al. (2008b) who studied 138 cows for 4 weeks, examining each cow each week. The cows were grouped into different management categories including dry cows and cows that had recently been on pasture, both factors previously reported as protective factors for DD (Dopfer et al., 2008; Somers et al., 2005a), which might have led to different infection pressures and dynamics in Holzhauer et al.'s (2008b) study compared with the present study, where cows were housed permanently. Despite the differences some useful information can be gleaned from comparing the two studies. Holzhauer et al. (2008b) reported that 31% (62/202) of healthy feet developed a lesion within the 4-week study, whereas in the present study approximately 49% of healthy feet developed a lesion during the 11-12 week observation period, a lower incidence per week. Possible explanations for this difference might be differences in the time period, infection pressure, environment, host or pathogen strain, stage of lactation, parity production level and other factors concerning the claw-health management (like foot baths). Holzhauer et al. (2008b) reported that 25% (35/142) of early lesions and 14% (28/194) of old lesions resolved within 4 weeks. In the present study, resolution was observed in 34% of lesions. Holzhauer et al. (2008b) did not report the duration of lesions and it could be argued that the low resolution rate, especially in old lesions, was because they lasted longer than the four weeks of observation. In the present study, the majority of recoveries occurred within the first two weeks of a disease event, but approximately 20% of disease episodes in which no resolution was observed lasted at least three weeks. Also, the mean duration of censored disease events in the present study indicates that some lesions might last for weeks even though the mean duration of uncensored disease events was shorter, this also indicates that certain cows had lesions that persisted.

The fact that the majority of resolutions occurred within the first two weeks of a disease event might indicate that the duration of DD lesions might be shorter than that reported in previous studies (Dopfer et al., 1997; Somers et al., 2005b; Nielsen et al., 2009). The fact that the majority (78%) of all transitions occurring in healthy feet were recorded directly to presumed late lesions (score 4 or 5) also indicates a possible shorter duration of early disease states than expected: the very low number of early lesions (score 1 & 2) suggest that these states might be very transient and therefore more difficult to detect with weekly observations. Furthermore, these lesions are typically small and thus easier to miss during observation.

There was between cow heterogeneity with some cows never affected and other cows with persisting lesions. The duration of the episode affected the hazard of a transition with the longer the episode the less likely a transition. This applied to occurrence as well as resolution of lesions. This finding supports the hypothesis presented by Dopfer et al. (2004) and Holzhauer et al. (2008a), where three types of individual dynamics were defined: unaffected cattle, single lesion cattle and the cattle with repeated, persisting lesions.

Studies on host differences are needed to identify factors that might affect these individual dynamics. In the present study some host factors were studied. Parity 2 cows seemed to be more likely to recover from lesions than parity 1 cows, and parity 3 cows had a reduced hazard of developing, and tended to have a higher likelihood of resolution from lesions compared with parity 1 cows. This is in agreement with earlier studies reporting that younger cows were more susceptible to DD than older cows (Barker et al., 2009; Holzhauer et al., 2008b; Somers et al., 2005b). Holzhauer et al., (2008a) reported that parity 1 and 2 cows were more likely to develop persistent lesions than older cows. This is supported by the higher probability of resolution in older cows compared with parity 1 cows in the present study. In the present study, cows in early lactation were less likely to develop lesions than cows in mid or late lactation. This is in contrast to earlier studies that report late lactation as protective for the risk of developing DD (Somers et al., 2005a; Holzhauer et al., 2008b; Barker et al., 2009). However, in the current study the duration of lesions in late lactation was shorter than in those in early lactation, so previous studies might have missed lesion occurrence because of the time between observations (Somers et al., 2005b) or because cows recovered before they needed treatment (Barker et al., 2009), thereby leading to the impression that lesions developed less frequently.

There was no significant effect on lesion occurrence or resolution from washing the left feet of the cows although washing tended to have a positive effect on resolution. It can be speculated that washing the feet might have reduced the infection pressure in the herd overall. If this is the case, the estimates in the present study would be underestimating the true incidence of lesions in either leg.

One explanation for some of the different risks in the current study to those reported in earlier studies is that several scoring systems have been used. In addition, in the current study only lesions on the plantar skin bordering the interdigital space (the heel region) was assessed, whereas other studies also recorded lesions at other sites (Dopfer et al., 2008; Holzhauer et al., 2008b). However, in most studies the plantar skin is the most common site for DD lesions. Finally, the current study reports the risks for transition from no lesion to a lesion and vice versa all within one model rather than separate models, providing a novel angle on previous research.

In the present study, left feet were washed and right feet were not. This difference in management between the legs could have biased the results. However, there were no significant differences between feet with foot included as a fixed effect and results were similar when left feet were excluded from the analysis. We therefore do not think that the automatic hoof washing had any substantial effect on the duration of lesions or disease states. For a thorough examination of the skin in the heel region both hind legs had to be washed manually at each recording. This meant that the right feet were washed once weekly during the study period, while the left feet were washed 15 times a week (twice daily in the automatic washing machine plus one manual washing). With a potential effect of weekly washing on the transitions between lesion scores and/or duration of DD lesions this might mean that effects of washing in the present study were underestimated.

Three trained observers took part in this study. This might have influenced the results from the study if a high degree of agreement between observers was not obtained. Thomsen et al. (2008) evaluated the sensitivity and specificity of scoring DD lesions during milking compared with scoring at hoof trimming and found it to be acceptable. To our knowledge, the inter- and intraobserver agreement of the DD scoring system used in the present study has not been formally tested. However, it has been shown that training and calibration improves the reliability of scoring systems where some degree of subjectivity is present (Kristensen et al., 2006). In the present study, the observers were experienced in using the DD scoring system and were trained before observations started, and we thus feel confident, that a good calibration and an acceptable degree of agreement was obtained.

In the present study, the dynamics of DD lesions were evaluated under normal conditions in three commercial Danish dairy herds. There were only three farms studied and farm B had lower levels of disease. No management factors were investigated so it is not possible to explain why the force of infection might have been lower on this farm, however, all analyses were done controlling for farm differences. The patterns of association between DD and the cow effects were consistent across all farms even if the absolute baseline value per farm varied. The herds had similar housing systems (although two had slatted and one had solid concrete floors) and in none of them the cows had access to outdoor areas. As part of the protocol of the clinical trial all cows were examined in a hoof trimming chute every six weeks and trimmed when needed and the three herds in the present study therefore had a hoof trimming shortly before and one hoof trimming (or examination) during the study period. We therefore expect that the state of the hooves was comparable between the farms. DD lesions could be treated by the farmer using their usual routine and the decision on when and how to treat DD lesions could therefore differ between herds. This might have influenced the duration of lesions. However, by including herd as a fixed effect in the model we control for treatment differences as well as other differences between herds.

Some consideration also has to be given the power of some estimates from the present study because there in some categories only were a small number of episodes. For example, only eight disease episodes ending in resolution lasted more than six weeks, which means that the parameter estimate of the effect of long duration on this particular transition is less robust than estimates based on more observations.

Conclusions

We conclude that cows are heterogeneous in their probability of occurrence and resolution of DD lesions in hind legs. The occurrence and resolution of DD lesions was also influenced by stage of lactation and parity. The majority of transitions between disease states occurred within two weeks, indicating that DD under the circumstances in the present study was a very dynamic disease and that the duration of the majority of DD lesions was shorter than the 42 days previously reported. Further studies with shorter observation intervals are needed to confirm this. The multilevel multistate discrete-time model was an appropriate method to evaluate the hazard of occurrence and resolution from DD lesions. With more data available, this methodology could also be suited to investigate the dynamics of the transitions between different disease states and heterogeneity between cows. The strength of multistate models is that multiple transitions from multiple original states, even with complex data with hierarchical structures, can be modelled simultaneously.

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Competing interests

The authors declare that they have no competing interests

Authors' contribution

BHN carried out the majority of the clinical examinations, participated in the design of the study, participated in the statistical analysis and drafted the manuscript. LEG and JK participated in the statistical analysis and helped to draft the manuscript. PTT participated in the design of the study, did part of the clinical examinations and also helped to draft the manuscript. All authors have read and approved the final manuscript.

Table 1: Herd characteristics in a study of digital dermatitis in 742 lactating cows in three commercial dairy herds: cows, milk production, mean number of cows per observation, mean distribution of cows in parity groups and lactation states and mean DD prevalence during the observation period

	Herd A		Herd B		Herd C	
Number of cows	195		212		353	
Milk production (kg ECM per cow per year)	9007		9477		9511	
	Mean	**Standard deviation**	**Mean**	**Standard deviation**	**Mean**	**Standard deviation**
Number of observations per week	147[a]	12.0	176[b]	13.7	274[c]	25.0
Parity						
1	49[a]	2.2	47[b]	2.5	53[c]	2.3
2	32[a]	1.7	26[b]	1.3	22[c]	1.3
3+	19[a]	1.6	27[b]	2.2	25[c]	2.3
Days in Milk (DIM)						
0-90	23[a]	3.9	18[b]	2.0	19[b]	2.0
91-180	25[a]	2.9	15[b]	1.5	26[a]	3.0
>180	52[a]	2.0	68[b]	1.9	55[c]	1.6
Prevalence of digital dermatitis						
Cow	0.35[a]	0.48	0.23[b]	0.42	0.30[c]	0.46
Left foot	0.23[1a]	0.42	0.13[b]	0.34	0.20[c]	0.40
Right foot	0.27[1a]	0.44	0.14[b]	0.35	0.21[c]	0.41
Number of feet affected						
One	61.7[a]	14.5	80.5[b]	9.4	65.5[a]	7.9
Two	38.3[a]	14.5	19.5[b]	9.4	34.5[a]	7.9
Number of recurring digital dermatitis lesions						
Cow	2.9[a]	1.6	2.4[b]	1.4	1.8[c]	0.9
Left foot	1.9[a]	0.9	1.6[b]	0.8	1.2[c]	0.5
Right foot	1.8[a]	0.9	1.6[a]	0.8	1.3[b]	0.5

Means within a row having different superscript letters differ ($p<0.05$)

1: DD prevalence between treated and non-treated feet differ ($p<0.05$)

Table 2: Lesion scoring of digital dermatitis lesions according to Manske et al. (2002) and categorisation of groups for the multistate model

Score	Original description	Regrouping for multistate model outcome	Number of observations by score (N_{total} = 10585)
0	No lesion	State 0 = No lesion	8159
1	Hyperaemic area with erected pili	State 1 = Lesion	1
2	Moist, exudative and hyperaemic area, with intact epidermis		56
3	Exudative area, exposed corium, with no signs of healing		759
4	Exposed corium but in process of healing, dried-up lesion		666
5	Dark brown scab, completely or almost completely healed lesion		944

Table 3: Number of observations (N = Count; % = Percent of total number of observations) of persistence or transitions between disease states by next observation by lesion score in a study of digital dermatitis in 742 lactating cows in three commercial dairy herds.

		Lesion score at next observation												
Origin state lesion score		**0**		**1**		**2**		**3**		**4**		**5**		
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**		**N**	**%**	**Total**
Left foot	**0**	3701	89.4	1	0.0	13	0.3	83	2.0	80	1.9	263	6.4	4141
	1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
	2	12	50.0	0	0.0	0	0.0	5	20.8	2	8.3	5	20.8	24
	3	82	21.9	0	0.0	5	1.3	168	44.9	73	19.5	46	12.3	374
	4	72	26.0	0	0.0	2	0.7	65	23.5	88	31.8	50	18.1	277
	5	242	50.0	0	0.0	10	2.1	30	6.2	45	9.3	157	32.4	484
	Total	4109		1		30		351		288		521		5300
Right foot	**0**	3535	88.0	0	0.0	23	0.6	79	2.0	125	3.1	256	6.4	4018
	1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	100.0	1
	2	13	40.6	0	0.0	1	3.1	5	15.6	7	21.9	6	18.8	32
	3	71	18.4	0	0.0	8	2.1	189	49.1	80	20.8	37	9.6	385
	4	109	28.0	1	0.3	1	0.3	73	18.8	143	36.8	62	15.9	389
	5	231	50.2	0	0.0	4	0.9	16	3.5	76	16.5	133	28.9	460
	Total	3959		1		37		362		431		495		5285

Table 4: Number of transitions between healthy and diseased states (uncensored episodes) in a study of digital dermatitis in 742 lactating cows in three commercial dairy herds.

Origin state		Transition state: No lesion	Lesion	Sum
Left foot	**No lesion**	3701	440	4141
	Lesion	408	751	1159
	Sum	4109	1191	
Right foot	**No lesion**	3535	483	4018
	Lesion	424	843	1267
	Sum	3959	1326	

Table 5: Number of types of transitions in the different categories of the explanatory variables from a multilevel, multistate model used in a study of digital dermatitis in 742 lactating cows in three commercial dairy herds

	Transition type		
	Occurrence	**Resolution**	**Sum**
Days in milk (DIM) at start of state			
0-90	252	221	473
91-180	308	284	592
>180	363	327	690
Parity			
1	458	417	875
2	294	256	550
3+	171	159	330
Duration of state (weeks)			
1	366	535	901
2	215	138	353
3-6	255	151	406
7+	87	8	95
Foot			
Left hind	483	424	907
Right hind	440	408	848
Herd			
A	403	345	748
B	262	208	470
C	258	279	537

Table 6: Mean and median duration in weeks (stratified by herd) of 832 uncensored and 286 censored episodes in a study of digital dermatitis in 742 lactating cows in three commercial dairy herds.

Episode type	Herd	N obs	Mean duration	SD	Median duration
Uncensored Resolution observed	A	345	1.6	1.1	1
	B	208	1.7	1.4	1
	C	279	1.9	1.3	1
Censored No resolution observed	A	106	3.0	2.4	2
	B	66	2.8	2.1	2
	C	114	4.4	2.8	4

Table 7: Results from the multilevel, multistate model used in a study of digital dermatitis in 742 lactating cows in three commercial dairy herds: Effects of parity, DIM, uncensored episode duration, foot and herd on the risk of transition from healthy to diseased state (occurrence) and from diseased to healthy state (resolution).

		DD lesion occurrence[ab]		DD lesion resolution[ab]	
Parameter		**Odds ratio**	**95% credibility interval**	**Odds ratio**	**95% credibility interval**
Parity					
	1	1		1	
	2	1.275	1.063 - 1.530	1.082	0.884 - 1.324
	3+	0.797	0.643 - 0.987	1.246	0.970 - 1.600
Days in milk					
	0-90	1		1	
	91-180	1.369	1.096 - 1.709	1.143	0.873 - 1.498
	>180	1.269	1.051 - 1.531	1.267	1.003 - 1.602
Duration (weeks)					
	1	1		1	
	2	0.783	0.644 - 0.953	0.412	0.326 - 0.522
	3-6	0.379	0.317 - 0.454	0.343	0.274 - 0.429
	7+	0.272	0.210 - 0.352	0.090	0.042 - 0.191
Foot					
	Right	1		1	
	Left	0.986	0.806 - 1.207	1.178	0.974 - 1.425
Herd					
	A	1		1	
	B	0.425	0.316 - 0.573	0.884	0.666 - 1.175
	C	0.384	0.302 - 0.490	0.608	0.481 - 0.768

a: Estimated random effects (Standard Error) - Model with duration effects only:

Intercept (occurrence) = -1.677 (0.102); Intercept (resolution) = -0.238 (0.070)

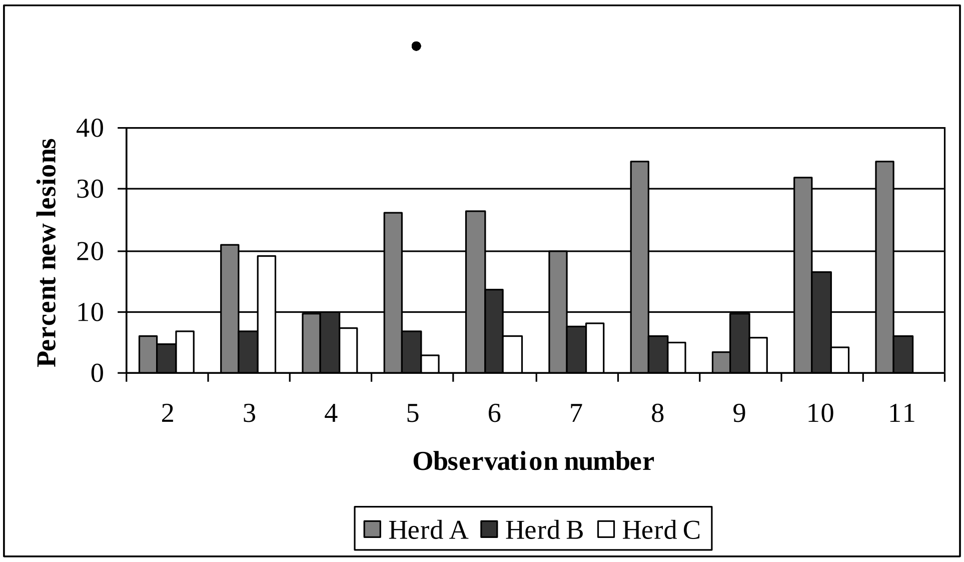
Random variability between cows: Lesion occurrence = 0.44 (0.11); lesion resolution = 0.065 (0.032)

b: Estimated random effects - Final model with covariates:

Intercept (occurrence) = -1.074 (0.163), Intercept (resolution) = -0.278 (0.184)

Random variability between cows: Lesion occurrence = 0.07 (0.04); lesion resolution = 0.06 (0.05)

Figure 1: Percent incident lesions (lesions in feet not affected the previous week) per observation week stratified by herd. (Herd C was only observed for 11 weeks).



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