

Regular Article

Markov chain approach to analyze the dynamics of pathogen fecal shedding—Example of *Listeria monocytogenes* shedding in a herd of dairy cattle

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Received 1 March 2006; received in revised form 25 July 2006; accepted 27 September 2006

Available online 7 October 2006

Abstract

Fecal shedding is an important mechanism of spreading of a number of human and animal pathogens. Understanding of the dynamics of pathogen fecal shedding is critical to be able to control or prevent the spread of diseases caused by these pathogens. The objective of this study was to develop a model for analysis of the dynamics of pathogen fecal shedding. Fecal shedding of *Listeria monocytogenes* in dairy cattle was used as a model system. A Markov chain model (MCM) with two states, shedding and non-shedding, has been developed for overall *L. monocytogenes* fecal shedding (all *L. monocytogenes* subtypes) and fecal shedding of three *L. monocytogenes* subtypes (ribotypes 1058A, 1039E and 1042B) using data from one study farm. The matrices of conditional probabilities of transition between shedding and non-shedding states for different sets of covariates have been estimated by application of logistic regression. The covariate-specific matrices of conditional probabilities, describing the presence of different risk factors, were used to estimate (i) the stationary prevalence of dairy cows that shed any *L. monocytogenes* subtype or ribotypes 1058A, 1039E, and 1042B, (ii) the duration of overall and subtype specific fecal shedding, and (iii) the duration of periods without shedding. A non-homogeneous MCM was constructed to study how the prevalence of fecal shedders changes over time. The model was validated with data from the study farm and published literature. The results of our modeling work indicated that (i) the prevalence of *L. monocytogenes* fecal shedders varies over time and can be higher than 90%, (ii) *L. monocytogenes* subtypes exhibit different dynamics of fecal shedding, (iii) the dynamics of *L. monocytogenes* fecal shedding are highly associated with contamination of silage (fermented feed) and cows' exposure to stress, and (iv) the developed approach can be readily used to study the dynamics of fecal shedding in other pathogen–host–environment systems.

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Keywords: Markov chain model; Logistic regression; Duration of fecal shedding; Silage; Stress

1. Introduction

Fecal shedding represents an important mechanism of spreading of a number of pathogens. Estimating the probability and the duration of pathogen fecal shedding and the influence of risk factors on that probability and duration are of fundamental importance in the control of diseases that use fecal shedding as a means of spreading.

Pathogen fecal shedding of an individual may change over time with interchanging episodes of shedding and non-shedding. This two-state (shedding and non-shedding states) dynamic process is also often accompanied by dynamic occurrence of risk factors (covariates) associated with fecal shedding, forming a complex two-state-covariate dynamic structure. Because of that, the analysis of pathogen fecal shedding requires an analytical tool capable of handling the multi-state and dynamic nature of fecal shedding and the dynamic nature of risk factors associated with it. Furthermore, the method should be able to predict the pattern of fecal shedding beyond the range and timeframe of available data. A variety of descriptive

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(statistical) techniques has been used to analyze fecal shedding data, many borrowed from survival analysis (e.g. Alali et al., 2004). Within the framework of survival analysis, the recurrent events analysis (Therneau and Grambsch, 2000) could be used to analyze the dynamic and intermittent nature of fecal shedding. However, because the time spent in a fecal shedding episode could be long relative to the time spent between shedding episodes, a recurrent events analysis may not be appropriate. Instead, a more suitable approach would involve development of multi-state models, where the focus is on the times spent in various states of shedding, and on transition rates between the states (McKay et al., 2006). Whether survival analysis is suitable for analysis of the multi-state and dynamic nature of fecal shedding or not, a general disadvantage of all descriptive techniques (including survival analysis) is their applicability to only the data set from which statistics have been calculated. Because of that there are no grounds other than expert opinion or experimental confirmation with which to determine if they can be used to assess the relationships in untested circumstances, i.e. in some other system (location/population), or even in the same system at another time (WHO, 2005). A group of models that generally allows predictions beyond untested circumstances are known as mechanistic (also known as explanatory and process) models. They are built by explicitly considering the processes that produce our observations (Ellner and Guckenheimer, 2006) and therefore could expand the range of the data to include any untested circumstances where the same process can be presumed to operate, i.e. in situations where no measured data are available or even where such measurements are impossible (WHO, 2005). A mechanistic approach suitable for analysis of systems whose behavioral characteristics involve multi-state and dynamic elements, such as fecal shedding data, is Markov chain (MC) analysis. An MC model is characterized by two components: states and transition probabilities, which are synonyms for variables and parameters. The probability of the transition from the current state of a MC model to another state is solely determined by the current state.

The objective of this study was to apply MC modeling to analyze the dynamics of pathogen fecal shedding, particularly to estimate the duration of pathogen fecal shedding and the prevalence of individuals that excrete the pathogen in feces under the presence of different risk factors. Fecal shedding of *Listeria monocytogenes* (LM) in a herd of dairy cattle was used as a model system. This pathogen–host–environment system was chosen because of convenience of gathering data (LM is commonly isolated from feces of dairy cattle (Nightingale et al., 2004)) and relevance to human health (cattle farms have been suggested as an important reservoir of human LM infections (Arimi et al., 1997; Nightingale et al., 2004)). Isolation of LM in feces of cattle may be indicative of clinically or subclinically infected animals (Gronstol, 1979; Loken et al., 1982; Wesley, 1999). In addition, LM from contaminated feed

may pass through an animal's digestive tract, without causing LM infection, and also be excreted through feces (Shepherd et al., 2000). While there is a strong indication that LM infection occurs as a consequence of consumption of LM in contaminated silage (Fenlon et al., 1996), it is unknown whether LM excreted by a cow could cause LM infection or passive shedding in other cows in the herd. A cow-to-cow transmission of LM infection seems unlikely because, even if LM is present at high levels in fecal material, a cow would likely have to ingest a considerable amount of fecal material to become infected (reviewed by Ivanek et al., 2006). It has been reported that stress, such as during transport, increases shedding of LM in feces (Fenlon et al., 1996). The duration of fecal shedding (either infected or pass through shedding) is not well understood. Similarly, it is unclear whether LM infection in cattle triggers immunity to new LM infections and how long this immunity may persist (reviewed by Ivanek et al., 2006).

To develop an MC model of LM fecal shedding, first we applied statistical tools (univariate analysis and logistic regression) to analyze how fecal shedding depends on time-dependent covariates (covariates whose values are subject to change with time), also referred to as predictor variables or risk factors. Next, the estimated probability of fecal shedding for a given set of covariates was translated into an appropriate transition probability of a homogeneous Markov chain (HMC) model to estimate the proportion of dairy cattle likely to shed LM in feces and the duration of LM fecal shedding. Finally, the covariate-specific HMC models were combined into a non-homogeneous Markov chain (N-HMC) model where the transition matrix of conditional probabilities varies over time depending on the presence of time-varying covariates, to study the day-to-day variability of the proportion of cattle likely to shed LM in feces. Before we proceed to the description of the developed modeling approach we would like to make clear that the purpose of the applied modeling was not to analyze the transmission of diseases that use fecal shedding as a means of spreading. Instead, the purpose was to analyze the dynamics of fecal shedding (dynamics of contagiousness) during infection or passive shedding, whose understanding could then complement development of models of disease transmission.

2. Materials and methods

2.1. Description of data

The data from an intensive longitudinal study of LM shedding and feed contamination previously described by Ho et al. (2006) were used. Briefly, in that study, a set of 25 randomly selected lactating dairy cattle from a herd of 52 cows, housed in a tie-stall barn, were used for daily collection of fecal samples from January 18–31, 2004 (denoted as days 1–14), from February 12–15, 2004 (denoted as days 26–29), on February 25, 2004 (denoted

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