Preventive Veterinary Medicine 124 (2016) 96–101

Contents lists available at ScienceDirect

Preventive Veterinary Medicine

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

Short communication

Fraction of bovine leukemia virus-infected dairy cattle developing enzootic bovine leukosis

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ARTICLE INFO

Article history:
Received 29 June 2015
Received in revised form
24 November 2015
Accepted 30 November 2015

Keywords:
Enzootic bovine leukosis
Incubation period
Bovine leukemia virus

ABSTRACT

Enzootic bovine leucosis (EBL) is a transmissible disease caused by the bovine leukemia virus that is prevalent in cattle herds in many countries. Only a small fraction of infected animals develops clinical symptoms, such as malignant lymphosarcoma, after a long incubation period. In the present study, we aimed to determine the fraction of EBL-infected dairy cattle that develop lymphosarcoma and the length of the incubation period before clinical symptoms emerge. These parameters were determined by a mathematical modeling approach based on the maximum-likelihood estimation method, using the results of a nationwide serological survey of prevalence in cattle and passive surveillance records. The best-fit distribution to estimate the disease incubation period was determined to be the Weibull distribution, with a median and average incubation period of 7.0 years. The fraction of infected animals developing clinical disease was estimated to be 1.4% with a 95% confidence interval of 1.2–1.6%. The parameters estimated here contribute to an examination of efficient control strategies making quantitative evaluation available.

1. Introduction

Bovine leukemia virus (BLV) is the causative agent of enzootic bovine leukosis (EBL). EBL can cause malignant lymphosarcoma (Bartlett et al., 2014); however, most infected cattle finish their productive lives without showing any clinical symptoms (Rodríguez et al., 2011). A typical BLV infection is characterized by a high proviral load and permanent antibody response (Juliana et al., 2013). Infection is detected in animals by serological testing, usually ELISA or agar gel immune diffusion tests, although some reports suggest that specific BLV variants escape antibody detection (Fechner et al., 1997). BLV is transmitted both vertically and horizontally within livestock populations. Vertical transmission occurs when infected dams pass the disease via the placenta, intrapartum, and colostrum to their offspring (Gutiérrez et al., 2011; Lassauzet et al., 1991). There are several routes for horizontal BLV transmission between cattle, including rectal palpation without changing gloves, the use of a single needle for multiple animals, dehorning, presence of blood-feeding insects (i.e., horse flies), and close contact between animals (Gutiérrez et al., 2014; Perino et al., 1990; Rodríguez et al., 2011). Because EBL is a blood-borne disease, preventing direct and indirect contact with infected blood is the most important measure for preventing the spread of BLV in cattle herds.

Many European countries have national programs controlling the spread of BLV infection, and as a result, their cattle population is relatively free from BLV (Rodríguez et al., 2011). In contrast, the USA, Canada, and Argentina reported a high prevalence of BLV infection (Anon, 2008; Nekouei et al., 2015; Trono et al., 2001). Furthermore, one report found that approximately 40% of dairy and 30% of beef cattle in Japan were infected with BLV (Murakami et al., 2013). The high prevalence of the disease economically affects farmers because of increased detection and condemning of cattle on farms and slaughterhouses (Bartlett et al., 2014). Kahrs (2001) also indicated that herds with high BLV prevalence sometimes have reduced production efficiency, increased culling rates, and higher incidence of clinical lymphosarcoma. Lymphosarcoma caused by EBL is a notifiable disease, but there is no legally binding national BLV control program in Japan. Therefore, an economically feasible program to prevent further spread of EBL in cattle herds and decrease the incidence of clinical development may be required to mitigate the economic impact to farmers.

In the present study, we aimed to determine the fraction of BLV infected dairy cattle that develop lymphosarcoma, as well as the length of the incubation period before clinical symptoms emerge. These parameters are key elements needed to understand EBL disease progression in cattle populations and evaluate control mea-

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http://dx.doi.org/10.1016/j.prevetmed.2015.11.019
0167-5877/

sures over the course of several years. These data will also be usable for simulation and modeling studies examining disease course with respect to population dynamics and diseases with long incubation periods, such as EBL. We followed a mathematical modeling approach, based on the maximum-likelihood estimation method, to determine these key parameters using the results of a nationwide serological survey and records of reported EBL cases from passive surveillance. Finally, we discuss the usefulness and limitations of the estimated parameters for future disease control.

2. Materials and methods

2.1. Data

The Ministry of Agriculture, Forestry and Fisheries in Japan collected information on reported cases of EBL between 2011 and 2012 from prefectural governments. These data were used to determine the overall scope of BLV infections in Japan's cattle population. EBL was detected at both farms and slaughterhouses in the reported cases. On farms, most cases were first suspected due to clinical symptoms, and then they were confirmed after serological testing or necropsy. At slaughterhouses, EBL cases were detected upon postmortem inspection with a confirmatory test, such as a histopathological examination. A descriptive analysis of this data was conducted at the National Institute of Animal Health (Ibaraki, Japan). In this analysis, there was no significant difference between 2011 and 2012 in the distribution of detected cases by region, age, and farm type, whereas the total number of detected cases increased in 2012.

In the present study, we used the reported EBL incidence in cattle up to 12 years of age; the reported incidence was obtained from the above-described descriptive analysis. The cases aged more than 12 years accounted for less than 1% of the total number of dairy cases. The ages of the infected animals were categorized into classes separated by periods of 6 months. To estimate age-dependent infections, we used data obtained from the nationwide serological survey conducted in 2010. Details of sampling and testing procedures were previously described in detail (Murakami et al., 2013). These data included age-dependent sero-prevalence of BLV infections in dairy cattle (Fig. 1). Survivorship of dairy cattle was obtained from the individual cattle identification system database stored at the National Livestock Breeding Center (Fukushima, Japan). This database provides individual identification numbers and ages (in months) of dairy cattle that died on farms or were slaughtered in the 2012 fiscal year (Anon, 2013). Information was obtained from cattle up to 12 years of age, assuming all cattle died or were slaughtered by this age. These cattle accounted for over 99% of the total dead or slaughtered dairy cattle in Japan.

2.2. Model building

2.2.1. Probability of BLV infection by age

The survey results indicate that the sero-prevalence of BLV consistently increases until 4.5 years old, with an initial prevalence of 20% in animals at 6 months of age (Fig. 1). If we assume the constant age specific sero-prevalence in the cattle population, fluctuations and plateauing of BLV infections in animals over 4.5 years old may be explained by the reason that these infected animals are culled earlier than other animals for a number of reasons, including poor milk production (Erskine et al., 2012; Bartlett et al., 2013). There is no specific biological explanation for the halt of horizontal transmission of BLV among older cattle. We assumed that the initial vertical infection and later horizontal infections continue until the end of age 12 with a constant probability of infection among susceptible animals in each 6-month age class. This constant probability was calculated from the increase in BLV sero-prevalence until age of 4.5 years old, assuming stable infection rates in the whole population. The probability of infection among susceptible animals over a 6-month period (λ) was estimated by fitting the observed proportion of susceptible animals (S) in each 6-month age class until 4.5 years of age using the following formula

$$S_t = (1-m)(1-\lambda)^t \qquad (1)$$

where, t is the number in sequential 6-month age classes from 0 to 24, and m is probability of maternal infection. For estimating λ in the above equation, t is examined only from 1 (0.5 years of age) to 9 (4.5 years of age).

2.2.2. Clinical stage animal detection on farms

On farms, the development of lymphosarcomas was determined by clinical examination of infected cattle. However, clinical signs associated with lymphosarcoma are highly variable (Nagy, 2012) and depend on tumor size and location. We defined the progression of BLV infection to the clinical stage as animals presenting with malignant lymphosarcoma and detectable disease symptoms, such as cervical swelling, lymphoid hyperplasia, protrusion of the eyes, or a cutaneous form of the disease consisting of multiple nodes and plaques on the skin (Nagy, 2012). It was assumed that a certain proportion of animals in the clinical stage were not detected on farms and were instead sent to slaughterhouses for early culling due to poor performance or body condition. Under these assumptions, the probability of detecting clinical-stage animals on farms in the 6-month age class t (Ft) is given as follows:

$$F_t = \mathrm{SV}_t \times \mathrm{c} \times (1-(D_t+\mathrm{SL}_t)) \times k \times \int_{a=0}^{t-1} i(a)g(t-a)da \qquad (2)$$

where, SV_t is the probability of survival until the end of the 6-month age class t -1; c is the fraction of infected animals progressing to the clinical disease stage, assuming it is independent of age; D_t is the probability of animals dying at the 6-month age class t ; SL_t is the probability of slaughter at the 6-month age class t ; k is the fraction of animals in the clinical stage detected on farms, assuming it is independent of age; $i(a)$ is the probability of infection at the 6-month age class a ; and g is the probability function of the incubation period. The probability of infection was then calculated using the estimated value of λ . Since λ is the probability of infection among susceptible animals, i(a) is calculated by multiplying λ with the probability of remaining susceptible animals in the 6-month age class a-1. For the probability of infection at the 6-month age class 0, the probability of maternal infection, m, the estimated value of 0.17 was used. The estimated probability of infection at the 6-month age class 1 is 0.040, and then this probability constantly decreases to 0.013 at the 6-month age class 24. For incubation period distributions, there was no previous information for EBL. Therefore, we evaluated three forms of distribution—gamma, Weibull, and log-normal to find the distribution that best fitted the observed data.

2.2.3. Clinical stage animal detection at slaughterhouses

We assumed that animals in both the clinical and preclinical stages were detected at slaughterhouses. There were two categories of animals detected in the clinical stage. One category included animals that developed clinical disease on farms and were then sent to slaughterhouses for early culling because of the disease. These clinically affected animals were not detected on the farm but in slaughterhouses. Therefore, these animals represent a fraction (1-k) of animals developing clinical symptoms on farms.