Preventive Veterinary Medicine 149 (2018) 38–46

Contents lists available at ScienceDirect

Preventive Veterinary Medicine

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

Evaluation of fecal shedding and antibody response in dairy cattle infected with paratuberculosis using national surveillance data in Japan

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ARTICLE INFO

Keywords:
Mycobacterium avium subspecies *paratuberculosis*
Johne's disease
Mathematical modeling
Fecal shedding
Antibody test
Surveillance

ABSTRACT

Paratuberculosis or Johne's disease (JD), is a chronic infectious disease causing intractable diarrhea in cattle, which leads to less productivity, such as decreased milk yield, and lower daily weight gain. As a control measure against JD in cattle, national serological surveillance has been conducted in Japan since 1998. To conduct modeling studies that are useful to evaluate the effectiveness of control measures against JD, reliable parameter values, such as length of time from infection to the start of fecal shedding or antibody expression, are especially important. These parameters in the Japanese cattle population are assumed to be different from those in other countries with a higher prevalence of JD or in experimental infection settings; therefore, they must be estimated for the cattle population in Japan. Data from national surveillance conducted in Tokachi District, Hokkaido Prefecture, were used for this study. Using data from JD diagnostic tests for all cattle in Tokachi District between 1998 and 2014, all testing histories for infected animals were estimated as the number of tested cattle and positive cattle at each age of month for both fecal and antibody tests. A deterministic mathematical model for JD development, from infection to fecal shedding and antibody expression in infected cattle, was constructed to obtain the probability of testing positive when applied to both fecal and antibody tests at a given age. Likelihood was obtained from these estimated test results and best values for parameters were obtained using the Markov Chain Monte-Carlo method. Fifty-five percent of infected cattle were projected to have a transient shedding period, which was estimated to start 12 months after infection and last for 4 months. Persistent shedding was projected to occur in all infected cattle, and estimated to begin 7–84 months from infection. Following persistent shedding, antibody expression was estimated to start 7 months later. These values are useful for developing models to evaluate the status of JD infection and the effectiveness of control measures in the Japanese cattle population.

1. Introduction

Paratuberculosis (Johne's disease [JD]) is a chronic infectious disease of ruminants caused by *Mycobacterium avium* subsp. *paratuberculosis* (MAP) (Behr and Schurr, 2006). After several years of infection, animals will develop intractable enteritis, which leads to loss of production (i.e., milk yield) and body weight (Behr and Collins, 2010; McAloon et al., 2015; Smith et al., 2015a,b). MAP is also considered to be a potential cause of chronic enteritis known as Crohn's disease in humans (Liverani, 2014; Naser et al., 2014). Therefore, JD is one of the major concerns of cattle producers worldwide (Geraghty et al., 2014; Khol and Baumgartner, 2012).

In Japan, the first case of JD was reported in an imported dairy cow that died in 1927. As JD became endemic across the country, it was added to the list of reportable animal diseases in the Domestic Animal Infectious Diseases Control Law in 1971. Subsequently, cattle found infected with MAP were subjected to compulsory destruction with compensation. In addition, national serological surveillance targeting MAP infection in cattle started in 1998 as a compulsory program enforced by law (Kobayashi et al., 2007). The national active surveillance program consists of two components: serological regular surveillance (RS) and follow-up surveillance (FS) for farms in which MAP infection is detected. In RS, animals older than 24 months of age in all target farms are serologically tested at intervals of less than five years. When

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https://doi.org/10.1016/j.prevetmed.2017.10.009
Received 2 May 2017; Received in revised form 18 October 2017; Accepted 18 October 2017

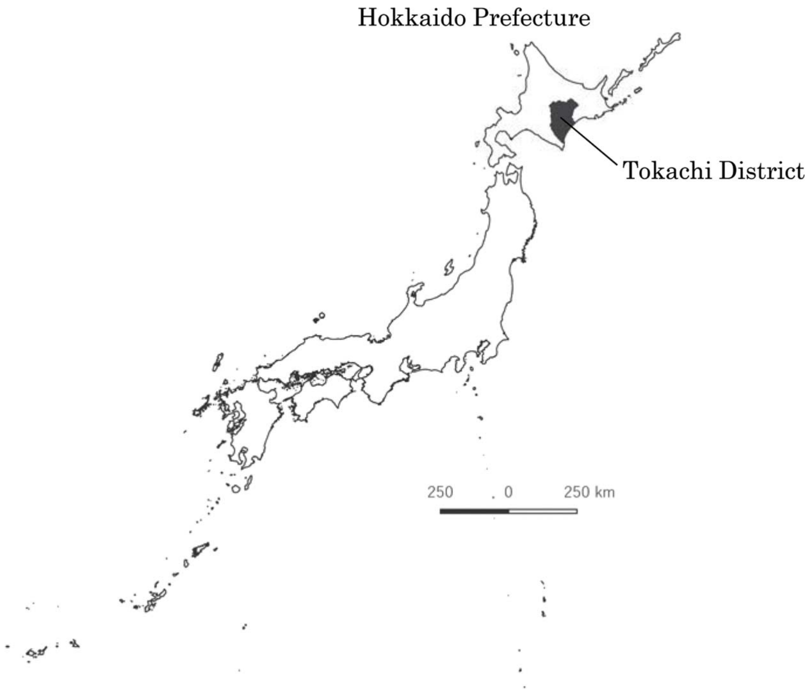

Fig. 1. Location of Tokachi District, Hokkaido Prefecture, Japan.

an infected animal is detected in RS, FS is conducted in those farms. In FS, blood and fecal samples are collected from all cattle older than 6 months of age for fecal and antibody tests performed at least five times within a three-year period. Affected farms regain free status if no additional cases are found in these tests. In addition, as a passive surveillance, all clinically suspected cattle are tested for blood and fecal samples the same way as conducted in FS. Since the beginning of the program, almost 500 thousand cattle had been tested annually nationwide and the total number of infected animals have been approximately 1000 every year.

As JD is an infection with a long incubation period of several years (Behr and Collins, 2010; Klinkenberg and Koets, 2015; Koets et al., 2015), and there is no available diagnostic test to detect all infected cattle, especially in the preclinical stage (Behr and Schurr, 2006; Nielsen and Toft, 2006), disease modeling techniques are suitable tool to evaluate disease prevalence or the effectiveness of control measures such as surveillance programs. When building transmission models, reasonable assumptions for parameter values are vital to obtain reliable results. Although several studies are available for reference parameter values needed for such models, most are from infection trials (Begg et al., 2010; Mortier et al., 2015a; van Roermund et al., 2007), or from naturally infected animals in countries or areas with a JD prevalence considerably higher than Japan (Benedictus et al., 2008; Nielsen, 2008; Nielsen and Ersbøll, 2006). Recent studies have reported that differences in infection setting (i.e., artificial/natural) (Mitchell et al., 2015) or the level of exposure at infection (Mortier et al., 2015a; Plattner et al., 2011) will influence the response of the hosts, such as bacterial excretion and humoral antibody response. Consequently, identifying parameter values specific to the Japanese cattle population is essential to develop reliable JD transmission models to analyze JD status in the country. Therefore, the aim of this study was to infer parameter values regarding JD development after infection (i.e., length of time from infection to fecal shedding and antibody expression) using empirical data from the national surveillance by applying the Markov Chain Monte-Carlo method (MCMC). The estimated values of these parameters will help to develop JD transmission models for the Japanese cattle population, and will provide further knowledge regarding the development of JD in cattle currently under intensive control programs.

2. Methods

2.1. Data preparation

In this study, we used test results from the national JD surveillance program conducted for almost 20 years in Tokachi District, Hokkaido Prefecture. In Hokkaido Prefecture, where almost one-half of dairy cattle in Japan are raised, all dairy and beef cattle farms are included in the JD surveillance program. Tokachi District, one of the mid-level government bodies including 19 municipalities, located in the south-eastern part of Hokkaido Island (Fig. 1), is known as the major dairy farming area in Japan, which has 1386 dairy farms with 222,482 cattle, including heifers and calves (Hokkaido Prefectural Government, 2016). The farm-size distribution of dairy farms in Tokachi District is 8, 65, 106, 190 and 710 corresponding to the 2.5, 25, 50, 75 and 97.5 percentiles, respectively, in February 2016 (personal communication, Hokkaido Prefectural Government, 2017). Records of all dairy cattle in which MAP infection was detected by all active and passive surveillance within the period from 1998 to 2014 in Tokachi District, were provided by the Hokkaido prefectural government.

Since the records only included testing histories when cattle were diagnosed as MAP infected, testing histories of negative results were completed for each animal using the following steps. Data for infected animals included date of diagnosis, test method, surveillance type used for detection, breed, sex, date of birth, farm identification number, and place of birth. The categories for surveillance type were defined as RS, FS, or tests for clinical suspicion. Given that RS started in April 1998, cattle born before April 1998 were removed from the analysis to assure that all animals analyzed were under the same JD control program during their lifetime. Information regarding the farms where these cattle were detected was also provided by the Hokkaido prefectural government. This information included farm type (i.e., dairy/beef), farm location (municipality) and, for farms that ceased operations, month and year of closure. Since RS was scheduled and conducted on a municipal basis in Tokachi District, all month(s)/year(s) when RS was conducted in each municipality was also provided. Using these data, all testing histories for each farm and each animal were estimated.

First, to estimate testing history for each farm, all month/year of