



Time series analysis based on two-part models for excessive zero count data to detect farm-level outbreaks of swine echinococcosis during meat inspections



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ABSTRACT

Echinococcus multilocularis is a parasite that causes highly pathogenic zoonoses and is maintained in foxes and rodents on Hokkaido Island, Japan. Detection of *E. multilocularis* infections in swine is epidemiologically important. In Hokkaido, administrative information is provided to swine producers based on the results of meat inspections. However, as the current criteria for providing administrative information often results in delays in providing information to producers, novel criteria are needed. Time series models were developed to monitor autocorrelations between data and lags using data collected from 84 producers at the Higashi-Mokoto Meat Inspection Center between April 2003 and November 2015. The two criteria were quantitatively compared using the sign test for the ability to rapidly detect farm-level outbreaks. Overall, the time series models based on an autoexponentially regressed zero-inflated negative binomial distribution with 60th percentile cumulative distribution function of the model detected outbreaks earlier more frequently than the current criteria (90.5%, 276/305, $p < 0.001$). Our results show that a two-part model with autoexponential regression can adequately deal with data involving an excessive number of zeros and that the novel criteria overcome disadvantages of the current criteria to provide an earlier indication of increases in the rate of echinococcosis.

1. Introduction

Echinococcus multilocularis is a tapeworm that causes alveolar echinococcosis, which is the most pathogenic and lethal parasitic zoonosis in the Northern Hemisphere (Eckert et al., 2000; Vuitton et al., 2003). Although swine are not considered an intermediate host in nature (Lukashenko, 1968, 1971) and humans do not acquire echinococcosis by ingesting infected pork, the detection of swine infected with *E. multilocularis* is significant from an epidemiologic point of view because the time period and area of infectious oocyst presence can be easily determined (Yagi et al., 2014). By contrast, it is very difficult to determine the source of infection in humans due to the long period from infection to onset of clinical symptoms. In swine, *E. multilocularis* infection is established by oral ingestion of oocysts derived from contaminated feces of red foxes, which often roam around swine operations due to the presence of food sources such as feed, placenta, and stillbirth tissues (Uraguchi and Takahashi, 1997; Yagi et al., 2014).

At the Hokkaido Higashi-Mokoto Meat Inspection Center, which

conducts meat inspections of livestock raised primarily in eastern Hokkaido, pig carcasses are inspected by gross pathologic examination. Carcasses in which the liver exhibits clear-boundary white nodules are diagnosed as having echinococcosis, and the livers are consequently condemned. A definitive diagnosis of *Echinococcus* infection is made on the basis of a periodic acid Schiff–positive cuticle layer (Sakui et al., 1984). *Ascaris suum* and nontuberculous *Mycobacterium* form similar white nodules, which can be differentiated by histopathology; fibrosis of Glisson's sheath and aggregation of eosinophils are seen in cases of ascariasis, and the nodules are stained using the Ziehl-Neelsen method in cases of mycobacteriosis. If the number of swine diagnosed with echinococcosis in a given month during meat inspections exceeds the standard criteria, the Meat Inspection Center informs the farm of the presence of *Echinococcus* infection in their swine and provides the farm with a brochure detailing preventive measures. The standard criteria are static thresholds for incidence rate and duration of echinococcosis and were adopted without consideration of a definition of an outbreak and without confirming the ability of the criteria to provide early

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detection. Therefore, alternative criteria developed according to a rational methodology are needed.

In this study, time series analysis was used to calculate the expected monthly number of swine livers condemned due to *Echinococcus* infection. Time series analysis is often used to evaluate sequential data in which measurements are equally spaced in time, such as meat inspection data (Neumann et al., 2014; Vial and Reist, 2014; Adachi and Makita, 2015a,b). However, the methods for time series analysis are so diverse that the appropriate method must be carefully selected based on the distribution of the data.

Data regarding the number of swine infected with *Echinococcus* are discrete variables with many zeros; therefore, Poisson regression models do not fit these data because the variance is much larger than the mean due to the excessive number of zeros. To properly address the problem of excessive zeros, several so-called ‘two-part models’ are often used, including the zero-inflated and hurdle models (Mullahy 1986; Lambert 1992). The idea behind these two-part approaches is that the outcome variable has a mixed distribution. A zero-inflated model assumes that the zero observations have one of two origins: sampling zeros due to a usual Poisson (or negative binomial) distribution and structural zeros due to a binomial distribution. A hurdle model assumes that the zero observations have one origin: structural zeros due to a binomial distribution (Hu et al., 2011). Although two-part models have been used to analyze a variety of data (Ghosh et al., 2006; Karazsia and van Dulmen, 2008; Moineddin et al., 2011; Cairns et al., 2013; Spiensma et al., 2013), few studies focusing on time series analysis using two-part models have been conducted (Yang et al., 2013; Huang et al., 2013; Imai et al., 2014). Furthermore, no research on time series analysis of meat inspection data using two-part models has been published.

The purpose of this study was to develop a method to predict the monthly number of *Echinococcus* infections detected per producer during meat inspections using time series analysis with the most appropriate distribution. The goal was to establish statistical criteria that enable the detection of unusual elevations in the number of infected swine.

2. Materials and Methods

2.1. Study design

The study compared a time series model and conventional criteria with regard to the speed and efficacy of detecting swine echinococcosis and sending administrative information to the producers for improvement of farm hygiene. First, the most suitable distribution was selected to model the monthly number of swine liver condemnations. Second, a time series model was developed to monitor autocorrelations between the data and lags. Finally, the data were statistically analyzed to quantitatively compare the two criteria among 84 producers in terms of the ability to rapidly detect farm-level outbreaks. Of these 84 producers, 50 were small scale (average monthly number of pigs brought < 100) and 44 were large scale (average monthly number of pigs brought ≥ 100). The source population was pig farms in eastern Hokkaido, Japan, and the target population was all pig farms in Japan. However, the results of this study can be extrapolated to a variety of temporal analyses of data with an excessive number of zeros. All statistical analyses in the present study were carried out using R software (version 3.1.3) (Ihaka and Gentleman, 1996).

2.2. Study area and data collection

The Higashi-Mokoto Meat Inspection Center is located in Abashiri-Gun, Hokkaido, Japan, and has two abattoirs that receive 150,000 to 200,000 pigs annually for slaughtering, mainly from eastern Hokkaido. Pig carcasses are inspected at this facility by gross pathologic examination, and carcasses in which the liver exhibits clear-boundary

white nodules are diagnosed with echinococcosis.

In this study, we used data from both abattoirs within the jurisdiction of the Higashi-Mokoto Meat Inspection Center, and data were collected between April 2003 and November 2015 (total of 2,317,430 swine heads transported by 143 producers). The monthly aggregate data from 84 producers (total of 1,397,608 heads during the entire period) in terms of the cumulative number of condemned livers were used for the study. These 84 producers transported swine to the abattoirs for at least 12 months, with at least one liver from a pig carcass condemned due to echinococcosis.

2.3. Selection of the distribution for the model

In order to select the proper distribution for the time series model, six distribution types (i.e., Poisson, negative binomial, zero-inflated Poisson [ZIP], zero-inflated negative binomial [ZINB], Hurdle Poisson [HP], and Hurdle negative binomial [HNB]) were fit to the data using maximum-likelihood estimation. Deviance was assessed to compare the goodness of fit between the distribution types. The deviance for the Poisson and negative binomial distributions was calculated using generalized linear models. The deviance for the ZIP, ZINB, HP, and HNB distributions was calculated using the zeroinfl or hurdle function in the pscl library (Zeileis et al., 2008). The ZINB and HNB distributions were selected (see Results) and used exclusively thereafter.

2.4. Development of the time series model

In the next step, selection of autocorrelated lagged data for explanatory variables (which do lag) and estimation of coefficients for these explanatory variables were performed to develop the time series models.

We assumed a time series model with a ZINB distribution, with the probability mass function given by Eq. (1):

$$P(Y_t = y_t) = \begin{cases} \omega_t + (1 - \omega_t)f(0) & (y_t = 0) \\ (1 - \omega_t)f(y_t) & (y_t > 0) \end{cases} \quad (1)$$

where $P(Y_t = y_t)$ describes the probability that the realization of the number of condemned livers Y_t at time point t is equal to y_t . The term ω_t represents the zero-inflation parameter at time point t , and $f(y_t)$ describes the negative binomial distribution given by Eq. (2):

$$f(y_t) = \frac{\Gamma(\theta + y_t)}{\Gamma(\theta)\Gamma(y_t + 1)} \left(\frac{\theta}{\theta + \lambda_t}\right)^\theta \left(\frac{\lambda_t}{\theta + \lambda_t}\right)^{\lambda_t} \quad (2)$$

where the term θ represents the dispersion parameter of the negative binomial distribution, and λ_t represents the expected value of the negative binomial distribution at time point t . We also assumed a time series model with an HNB, with the probability mass function given by Eq. (3):

$$P(Y_t = y_t) = \begin{cases} \omega_t & (y_t = 0) \\ (1 - \omega_t) \frac{f(y_t)}{1 - f(0)} & (y_t > 0) \end{cases} \quad (3)$$

where $f(y_t)$ describes the negative binomial distribution shown in Eq. (2).

We modeled the parameters λ_t and ω_t of the ZINB and HNB distributions using Eqs. (4) and (5) as:

$$\log \lambda_t = \beta_0 + \sum_{i=1}^q y_{t-i} \beta_i \quad (q \leq 12) \quad (4)$$

$$\text{logit}(\omega_t) = \gamma_0 + \sum_{i=1}^q y_{t-i} \gamma_i \quad (q \leq 12) \quad (5)$$

where the terms β_0 and γ_0 represent the intercepts of the regression equations. The terms $\beta_1, \beta_2, \beta_3, \dots, \beta_{12}$ and $\gamma_1, \gamma_2, \gamma_3, \dots, \gamma_{12}$ represent the regression coefficients. Rewriting Eqs. (4) and (5) gives:

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