Title: Time series analysis of human and bovine brucellosis in South Korea from 2005 to 2010

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Abstract

Brucellosis is considered to be one of the most important zoonotic diseases in the world, affecting underdeveloped and developing countries. The primary purpose of brucellosis control is to prevent the spread of disease from animals (typically ruminants) to humans. The main objective of this study was to retrospectively develop an appropriate time series model for cattle-to-human transmission in South Korea using data from independent national surveillance systems. Monthly case counts for cattle and people as well as national population data were available for 2005-2010. The temporal relationship was evaluated using an Autoregressive Integrated Moving Average with exogenous input (ARIMAX) model [notated as ARIMA (p, d, q) – AR(p)] and a Negative Binomial Regression (NBR) model.

Human incidence rate was highly correlated to cattle incidence rate in the same month and the previous month (both r = 0.82). In the final models, ARIMA (0, 1, 1) – AR (0, 1) was determined as the best fit with 191.5% error in the validation phase, whereas the best NBR model including lags (0, 1 months) for the cattle incidence rate yielded a 131.9% error in the validation phase. Error (MAPE) rates were high due to small absolute human case numbers (typically less than 10 per month in the validation phase). The NBR model however was able to demonstrate a marked reduction in human case immediately following a hypothetical marked reduction in cattle cases, and may be better for public health decision making.

Keywords

brucellosis; time series; lag; ARIMAX model; NBR model

1. Introduction

Brucellosis is considered to be one of the most important zoonotic diseases by the World Health Organization (WHO), Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE) (Joint FAO/WHO, 1986; Schelling et al., 2003). Infection with *Brucella abortus* in cattle causes abortions, infertility, and reduced milk production and can cause septicemic and/or granulomatous disease in humans (Halling and Boyle, 2002; Seleem et al., 2010). The primary objective of brucellosis control is to prevent human infections via disease control or eradication in animals. Humans can be easily infected with the *Brucella* organism through direct contact with milk, blood, tissue, or body fluids related to abortion in infected animals. The consumption of unpasteurized milk and cheese has historically been a major source of human infection in many countries (Olsen and Tatum, 2010). The onset of clinical signs in humans is generally a week or month after contact with infected animals or materials, although some infections cause minimal clinical illness (Young, 1983; WHO, 2006). Occupations with animal contact, such as farm workers, veterinarians, ranchers, abattoir workers and lab workers are classified as high risk groups (Seleem et al., 2010). Direct human-to-human transmission rarely occurs, although it has been reported that transmission may occur via breast-feeding and sexual contact (Arroyo et al., 2006; Kato et al., 2007). Disease control in humans is therefore accomplished by disease control in animals.

The South Korean government in their Infectious Disease Prevention and Control Act designated brucellosis as a reportable disease in both humans and animals (Kakoma et al., 2007; Wee et al., 2008). The first case of bovine brucellosis in the country was reported among imported dairy cattle in 1955 (Park and Lee, 1959). There has been a steady increase in the number of confirmed cases since the mid-1980s (Wee et al., 2008). Although there has been a national eradication program since the 1960s, an active surveillance program for brucellosis was not implemented before the 2000's (Yoo et al., 2009). The first human case in South Korea was officially reported in 2002, in a farm worker following the consumption of unpasteurized milk (Park et al., 2003). Thereafter, the number of human cases rapidly increased (Kim et al., 2006). In 2004, a new intensive brucellosis eradication program covering all dairy and beef cattle was launched. In South Korea, most human cases are related to not wearing protection, e.g. gloves, goggles and protective clothing, when in contact with suspected cattle or materials; but the consumption of raw milk and cheese is not common (Park et al., 2005).

Due to the zoonotic and economic aspects of this disease, count data are commonly collected for cattle and for human cases – typically through separate surveillance systems. Although monthly counts of human and cattle cases have been collected for several years in South Korea, the temporal relationship in the counts between species in the country has not been assessed. The relatively recent initiation of eradication programs in South Korea provided an opportunity to investigate the relationship between cattle and human count data obtained through independent systems. This type of time series data can be analyzed using an Autoregressive Integrated Moving Average (ARIMA) and Poisson [or Negative Binomial regression (NBR)] models. The different models have been used to analyze the time series data depending on their advantages and suitability. It was hypothesized that such a relationship could be quantified in a time series model and that such a model might have utility in predicting the impact of a reduction in cattle cases upon human case counts. The main objective of this study was to retrospectively develop an appropriate time series model of human and bovine brucellosis in South Korea using two methods and to compare their predictive capabilities.

2. Materials and methods

2.1. Data sources

National human and cattle population data were collected by the Korean Statistical Information Service (KOSIS) on a yearly and quarterly basis, respectively. Human and cattle cases were collected on a monthly basis by the Korea Centers for Disease Control and Prevention (KCDC) and the Animal Infectious Disease Data Management (AIMS), respectively. Both of these systems are operated by the South Korean government. Human case information was collected by passive surveillance. If humans were diagnosed with brucellosis at local or university hospitals, these cases were reported to the local public health authorities and captured into the central system of the KCDC. Cattle cases were reported by active and passive surveillance systems at the farm level. Dairy herds were tested six times a year using milk ring testing. If there were positive results, blood samples were collected and tested using the Rose-Bengal plate agglutination test. The beef cattle are tested twice a year on all farms that had more than 10 beef cattle using the Rose-Bengal plate agglutination test. In addition, slaughterhouse and pre-movement testing (between farms and markets) were mandatorily conducted. All the positive samples were retested using a serum agglutination test as a confirmatory test. Also, suspected cases were voluntarily reported to the authorities or veterinarians for laboratory testing. Laboratory testing of bovine samples was conducted at the National Veterinary Research and Quarantine Service, a World Organization for Animal Health (OIE) reference laboratory for brucellosis.

Since June 2004, intensive national surveillance and control measures (such as a brucellosis-free certificate system for sale or slaughter) have been conducted in all cattle. Therefore, we expected that the estimation of national cattle cases of brucellosis has become more accurate since 2004. Human and cattle case counts as recorded by the KCDC and AIMS, respectively were collected for the 6-year period from Jan 1, 2005, through Dec 31, 2010. From KOSIS, national human and cattle population data were obtained. All data sets were imported through Microsoft Excel 2007 (Redmond, WA, USA).

2.2. Time series analysis

The incidence rates for human and cattle were calculated on a monthly basis (cases / national total population) and reported per 100,000 population. In order to compute the incidence rates on a monthly basis, it was assumed that the national human and cattle population were constant on a yearly and quarterly basis, respectively, during this study period. Both crude incidence rates were used in the models. The human and cattle case datasets were divided into model construction (2005-7) and validation (2008-10) phases.

A time series ARIMAX model was first constructed, because it is statistically well developed and sophisticated model dealing with time series data. The ARIMAX model is an extension of the autoregressive integrated moving average (ARIMA) model, where external covariates may be added depending on cross-correlations between them and the response variable. Thus, an ARIMAX model was used because the cattle incidence rate should be included in the ARIMA model as an additional covariate. The common notation for the ARIMAX model is ARIMA(p, d, q) – AR(p), which is explained below. The stationarity of human incidence rate was assessed by plotting an autocorrelation function (ACF) (Diggle, 1990). Due to a lack of stationarity, the first order differencing was used with the purpose of stabilizing the response variable. Next, for assessing seasonality, a time sequence plot was used to identify any periodic fluctuations on a monthly basis. Once stationarity and seasonality were assessed, a univariate ARIMA model was initially developed with the response variable only dependent on its previous values and some random shocks (Box et al., 1994). The ARIMA model was determined by three parameters (p, d, and q): p was the number of autoregressive (AR) terms, d the number of times the model was differenced, and q the number of moving average (MA) terms. The common notation for such a model is ARIMA(p, d, q). The numbers of AR and MA terms needed were determined by analyzing the partial autocorrelation function (PACF) and ACF plots for the time series of human incidence rate (Lopez-Lozano et al., 2000; Wangdi et al., 2010). Lastly, external covariates (cattle incidence rate) were included in the model after analyzing cross-correlations between human and cattle incidence rates at various lags. For the model diagnostics, residuals were checked using autocorrelation plot and Ljung-Box test for independence (Ljung and Box, 1978).

Although a Poisson regression model is also commonly used in count data and thus was considered as a comparison model in the study, the Poisson model may not compensate for overdispersed count outcomes. Instead, a negative binomial regression (NBR) model can take into consideration the overdispersion count outcome variables (Long, 1997 and Dohoo et al., 2009). A likelihood ratio test was conducted to compare the Poisson and negative binomial models for the presence of overdispersion, and the test confirmed the presence of overdispersion. Therefore, for comparison to the ARIMAX model, collected data were also analyzed using a negative binomial regression (NBR) model. Cross-correlations between the human and cattle incidence rates at various lags were analyzed (Wang and Jain, 2003), and numerous models were developed by adding different lags in the cattle incidence rate. Variables with *P*-values < 0.05 were considered to be significant in any model.

The best fitting model was determined by comparing values of the Akaike Information Criterion (AIC) and overall pattern among different models (Diggle, 1990 and Dohoo et al., 2009). Predicted values and Mean Absolute Percentage Error (MAPE) were calculated using the formula for MAPE ($\frac{100\%}{n}\sum_{t=1}^{n}\left|\frac{\text{Actual cases}-\text{predicted cases}}{\text{Actual cases}}\right|$). Lastly, using the best ARIMAX and NBR models, we conducted simulation intervention scenarios (with 50% and 75% reductions in cattle cases) to predict how human case numbers would decline if cattle cases declined x% per month. Data analyses were conducted using STATA version 11.2 (StataCorp, College Station, Texas, USA).

3. Results

3.1. Descriptive data

The human population of South Korea increased from 48,138,000 in Jan 2005 to 49,410,000 in Dec 2010 (2.64% increase) whereas the cattle population increased by 62.01% in the same period (2,069,000 in Jan 2005 to 3,352,000 in Dec 2010). During the 6-year period, a total of 587 human and 74,493 cattle cases were recorded by the KCDC and AIMS, respectively. Absolute case counts per month ranged from 3,297 (September 2006) to 173 (December 2010) for cattle, and from 30 (September 2006) to 0 (November 2009, February and December 2010) for humans. Monthly human and cattle incidence rates are shown in Figure 1. Overall, incidence rates for both species appeared to have similar patterns. Incidence rates of brucellosis in both humans and cattle seemed to peak in September 2006, and since then have been decreasing. Human and cattle cases were relatively high between the months of March and September compared to other months (Table 1).

3.2. ARIMAX models

First differencing was used to achieve stationarity of the response variable (human incidence rate), and seasonality was not subsequently demonstrated (not shown). After the first differencing of the response variable, the ACF & PACF plots (not shown) suggested that a combination between MA (1) and AR (1) terms could be added in the model. The potential models for ARIMA in human incidence rate were ARIMA (0, 1, 0); ARIMA (1, 1, 0); ARIMA (0, 1, 1); and ARIMA (1, 1, 1). In addition, various lags of cattle incidence rate were included in the model based on cross-correlations. The strongest correlations were detected at the lag of 0 and 1 months (Table 2), thus the human incidence rate was most strongly correlated with the incidence rate of cattle in that same month and one month previous ($r=0.82$ for both months). Including AR (0) or AR (1) or AR (0, 1) in cattle incidence rate as external covariates demonstrated good fit, although the ARIMA (0, 1, 1) – AR (0, 1) model was considered to be the best due to slightly smaller AIC with better MAPE. The equation of this ARIMAX model was:

ARIMA (1, 1, 1) in human incidence rate – **AR** (0, 1) in cattle incidence rate

$$\hat{Y}_{t(HIR)} = \text{ARIMA}\left[\text{Constant} + Y_{t-1} + \phi((Y_{t-1} - Y_{t-2})) - \theta e_{t-1}\right] + \text{AR}\left[\ \beta_{t-1}X_{t-1} + \beta_t X_t\ \right]$$

Where $\hat{Y}_{t(HIR)}$ = the predicted human incidence rate at time t

Y_{t-1} = the human incidence rate at time t-1

Y_{t-2} = the human incidence rate at time t-2

e_{t-1} = unpredictable factors at time t-1 (a randomly generated number" when $\delta \sim N(0, 1)$)

X_{t-1} = the cattle incidence rate at time t-1

X_t = the cattle incidence rate at time t

This model could be interpreted as the relationship between the currrent occurrence of human cases and the unpredictable factors in the previous month with lags of 0 and 1 month for the cattle incidence rate. The diagnostic tests showed that all of the residual autocorrelations up to the lag of 27 were within the 95% confidence interval (CI) and the Ljung-Box test for the same 27 autocorrelations was not significant either (not shown). Using the data from the construction phase this model can be written as (Table 3):

$$\hat{Y}_t = [\ 8.13\text{x}10^{-11} + Y_{t-1} + 1.84\text{x}10^{-4} X_t + 1.85 \text{ x } 10^{-4} X_{t-1} + 0.86\ e_{t-1}\,] \text{ x } Y_{popt}$$

Where $\hat{Y}_t$ = the predicted number of human cases at time t

Y_{t-1} = the human incidence rate at time t-1

X_t = the cattle incidence rate at time t

X_{t-1} = the cattle incidence rate at time t-1

e_{t-1} = unpredictable factors at time t-1

Y_{popt}= the human population at time t

Using this model, predicted human cases were plotted with actual human cases (Fig. 2). No prediction was made for the first two observations, because there was no input data to predict for January and February 2005. Overall, the predicted cases followed a similar pattern of actual cases, and the ARIMAX model in the validation phase showed a decreasing pattern (Fig. 2) with 191.50% error in prediction. Using specific months with both high and low case numbers as examples, we were able to predict 26.12 and 2.12 cases from this model in Sep 2006 (30 cases actual) and July 2010 (5 cases actual), respectively. Equations were as follows:

$$26.12 \text{ (Predicted cases in Sep 2006)} = [8.13 \times 10^{-11} + 6.00 \times 10^{-7} + 1.84 \times 10^{-4} \times 1.28 \times 10^{-3} + 1.85 \times 10^{-4} \times 1.33 \times 10^{-3} + 0.86 \times e_{Aug2006}] \times 48{,}372{,}000$$

$$2.12 \text{ (Predicted cases in July 2010)} = [8.13 \times 10^{-11} + 1.01 \times 10^{-7} + 1.84 \times 10^{-4} \times 1.30 \times 10^{-4} + 1.85 \times 10^{-4} \times 0.15 \times 10^{-4} + 0.86 \times e_{Jun2010}] \times 49{,}410{,}000$$

Using this model, hypothetical reductions in cattle cases were employed to simulate large-scale brucellosis control/eradication methods and to evaluate predicted human case counts. Marked by-month reductions in cattle cases of 50% or 75% in the ARIMAX model did not result however in marked reductions in predicted human cases.

3.3. NBR models

The strongest correlations were demonstrated at the lag of 0 and 1 months based on the cross correlation between human and cattle (Table 2). Containing lags of (0, 1) months for cattle incidence rate (Table 4) provided the best model based on the smallest AIC and MAPE compared to models containing different lags in cattle incidence rate. In order to make a comparison with ARIMAX best model, lag 1 of human incidence rate was forced into the model, but this variable was marginally significant (Table 4). The NBR model equation was:

$$\ln \mathrm{E}(I_{t(\mathrm{HIR})}) = \ln\left(\frac{E(Y_t)}{n_t}\right) = \beta_0 + \beta_t \ln X_t + \beta_{t-1} \ln X_{t-1} + \cdots + \beta_{t-p} \ln X_{t-p}$$

Where $\ln \mathrm{E}(I_{t(\mathrm{HIR})})$ = the log of the predicted human incidence rate at time t

$\mathrm{E}(Y_t)$ = the expected number of human cases at time t

n_t = human population at time t

$\ln X_t$ = the log of the cattle incidence rate at time t

The best fitting model was demonstrated and this model can be written as:

$$\hat{Y}_t = \text{Exponential function}[(-7.33 + 0.52\ln(X_t) + 0.54\ln(X_{t-1})] \times Y_{popt}$$

Where $\hat{Y}_t$ = the expected number of human cases at time t

X_t = the cattle incidence rate at time t

X_{t-1} = the cattle incidence rate at time t-1

Y_{popt} = the human population at time t

From the two models in table 4, predicted human cases were plotted with actual human cases (Fig. 3). The first observation (January 2005) was not able to predict due to lack of input data. Overall, predictions from both models followed a similar pattern of actual cases, and the NBR model for the validation phase also showed the decreasing pattern of human cases (Fig. 3) with 131.88% error in prediction. Using months with both high and low case numbers as examples, we were able to predict 27.57 and 2.58 cases from this model in Sep 2006 (30 cases actual) and July 2010 (5 cases actual), respectively. Equations were as follows:

$$27.57 \text{ (Predicted cases in Sep 2006)} = \text{Exponential function } [(-7.33 + 0.52\ln(1.33 \times 10^{-3}) + 0.54\ln(1.28 \times 10^{-3})] \times 48{,}372{,}000$$

$$2.58 \text{ (Predicted cases in July 2010)} = \text{Exponential function } [(-7.33 + 0.52\ln(1.46 \times 10^{-4}) + 0.54\ln(1.30 \times 10^{-4})] \times 49{,}410{,}000$$

From the best model, hypothetical reductions in cattle case counts were employed to simulate effective brucellosis control/eradication methods and to evaluate predicted human case counts. Marked by-month reductions in cattle cases of 50% or 75% in the NBR model also yielded marked reductions in predicted human cases.

4. Discussion

Data accumulated in South Korea for 6 years was used to assess the feasibility of developing time series models using the temporal changes in human and bovine brucellosis in the country. Both human and cattle incidence rates of brucellosis peaked in September 2006 and since then have dramatically decreased, demonstrating effective eradication and control measures. An initial increase in cases in both species during the 2000's might have been due to the increased public awareness of the disease, possible increased physician recognition, and increased testing for brucellosis. The continuous disease monitoring efforts for bovine brucellosis implemented since 2000 have been able to detect more cases in asymptomatic and symptomatic cattle. More cases in cattle and in human were detected between the months of March and September during the study period. This finding is somewhat influenced statistically by the number of cases in the first half of the study period, but may also be related to cattle breeding and subsequent timing of abortions. Colder temperatures might also cause some reduction in infective organisms, thereby slightly diminishing the risk of zoonotic transmission during these months.

We constructed different models using two methods that could also be used to predict human cases from zoonotic transmission. The strongest correlation (r=0.82) for human cases was detected for the lags of 0 and 1 month in cattle incidence rate which is consistent with a short incubation period, i.e. most human infections appear to be occurring within a month of exposure (Young, 1983; WHO, 2006), and rapid diagnosis of the disease. This short lag time however also influences the capability to construct time series models for brucellosis for future prediction.

The ARIMAX model might be considered biologically unreasonable because the lag of 1 month in human incidence rate always remained in the model due to the first differencing. Although this lag could be interpreted as brucellosis in humans being transmitted by infected humans, no human-to-human cases have ever been reported in South Korea. Unpredictable factors were included as a so-called random shock, interpreted as factors that might influence the transmission of brucellosis from cattle to humans. Transmission from cattle to humans should theoretically yield models in which cattle incidence rates are the most significant variable for predicting human cases. In our models however the value of the human incidence rate in the preceding month was mathematically a much more important variable than the cattle incidence rate in human case predictions. Using the best-fit ARIMAX model, scenarios based on monthly reductions (50% or 75%) in cattle cases did not predict a timely reduction in human cases. Thus the ARIMAX model did not show a zoonotic benefit to humans from reducing cattle brucellosis cases. Although somewhat affected by the absolute number of cattle cases (previous or current month), it may be true that the human cases are more influenced by other risk factors in South Korea.

A NBR model appeared to be slightly superior to an ARIMAX model in this study, yet similarly included lags (0, 1 month) for the cattle incidence rate. In the simulation scenario, a monthly reduction (of 50% or 75%) in cattle cases directly decreased the number of human cases. Based on this analysis, the NBR model was considered more realistic and consistent with knowledge of brucellosis transmission, whereas the predictions of the ARIMAX model were highly affected by the human cases in the previous month due to the first differencing. Interestingly, in the NRB model, adding a lag of 1 month in human incidence rate was marginally significant (P=0.053). It could be interpreted as this Y_{t-1} variable might be a proxy for other possible factors, e.g. environmental risk factors, which were not taken into account in the model.

The assumption that human and cattle populations were constant on a yearly and quarterly basis, while not fully accurate, was considered to result in a non-differential bias because the relatively large denominators had minimal impact on monthly incidence rate as a covariate in the models. In contrast, small absolute numbers of human cases influenced calculations of mean absolute percentage error. The validated best NBR model showed a 131.88% error level whereas the validated best ARIMAX revealed a 191.50% error level although the error typically represented less than 8 human cases per month. Overall, in both best models, the relatively large MAPEs were due to fewer reported human cases during the time period used as the validation phase.

A limitation of the study potentially lies in not being able to utilize data at the individual province level. The major administrative areas in South Korea are its 7 metropolitan cities and 8 provinces. The majority of the cattle population is raised in the provinces, so provinces are more likely to have more cattle cases compared with metropolitan areas (Omer et al., 2000; Yoo et al., 2009). At-risk people from those provinces however may seek medical care/diagnoses in nearby metropolitan areas due to greater availability of hospital resources. Thus a more refined location of human cases may not accurately denote the exposure location. Also, other possible risk factors should be considered in a future study. Some studies have suggested that varied environmental risk factors should be taken into consideration. For instance, in studies from Germany (Dahouk et al., 2007), Denmark (Eriksen et al., 2002) and the United States (White and Atmar, 2002), more cases were reported in the summer season due to the higher likelihood of travel and more opportunity to come in contact with infected dairy products.

A recognized limitation was that the exposure history of human brucellosis cases was not available, restricting our ability to adjust for incubation periods or delayed recognition in individuals. This limitation is common in surveillance using aggregate data from independent systems. Misclassification bias due to incorrect diagnoses, i.e. false positives, was considered low both in humans and cattle due to the medical capabilities and the OIE reference laboratory for brucellosis in South Korea.

ARIMA models have been traditionally used in econometrics; however, their use is increasing in medical fields (Benschop et al., 2008; Soebiyanto et al., 2010; Wangdi et al., 2010). This study included the application of a simple ARIMAX model to predict human cases of brucellosis based on cattle cases. The major advantage of this model is that it takes into consideration seasonal differences, which might be useful to predict such as vector-borne diseases (Silawan et al., 2008; Wangdi et al., 2010).

Although the Poisson regression model has been commonly used in count data, it could be a problematic in this case since the mean and the variance are not equal (overdispersion). Therefore, a NBR model has been suggested in which the variance is not equivalent to the mean. The benefit of NBR is that it is less sophisticated to develop the model as compared to the ARIMAX model. Therefore, if the correlated errors are not a significant problem, an NBR model could be convenient to identify the temporal relationship.

5. Conclusion

The main objective of this study was to develop an appropriate time series model of human and bovine brucellosis in South Korea, and then provide a prediction model to the public health policy makers, physicians, and veterinarians involved in the control or prevention of brucellosis. The close temporal relationship of cattle and human cases restricted the utility of these models in prediction, yet this study affirmed the strong correlation between monthly case counts for the two species. Actions to reduce bovine brucellosis therefore had near immediate effects in also reducing human cases in this retrospective study. A negative binomial regression model should be considered in analyses of brucellosis using time series modeling.

Conflict of interest statement

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