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Original Article

Temporal trends and prediction of bovine tuberculosis: a time series analysis in the North-East of Iran

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Abstract

Background: Bovine tuberculosis (BTB) is a disease with high economic relevance. **Aims:** This study aimed to determine a fast alert surveillance system for bTB before the outbreak in the epidemic region of Iran. **Methods:** This cross-sectional study was conducted using the Auto-Regressive Integrated Moving Average (ARIMA) model for monthly bTB detections (reactors). These reactor cases result from the positive Tuberculin Purified Protein Derivative (PPD) test on cattle farms for the period between April 2007 and March 2019 in Razavi Khorasan province. Autocorrelation functions (ACF) and partial autocorrelation functions (PACF) plots were used to determine model parameters. The Akaike Information Criteria (AIC) were employed to select the best-fitted model. The root mean square error (RMSE) was applied for the evaluation of the models. Then, the best-fitted model was hired to predict the cases for 12 oncoming months. The data were analysed by STATA (ver. 14) software with a significant level at $P \leq 0.05$. **Results:** ARIMA (3, 0, 3) 12 was introduced as a recommended fitted model according to white noise residual test (Q=22.87 and P=0.98), lower AIC (541.85), and more precise model RMSE (1.50). However, the forecast values were more than the observed values. **Conclusion:** The application and interpretation of ARIMA models are straightforward, and may be used as immediate tools for monitoring systems. However, we proposed an Auto-Regressive Integrated Moving Average with Exogenous Input (ARIMAX) model with some measurable exotic factors such as economic fluctuations, climate changes, and pulmonary tuberculosis to introduce a more precise and accurate model for the fast alert surveillance system.

Key words: Bovine tuberculosis, Forecasting, Surveillance system, Time series analysis

Introduction

Cattles and other bovids were the primarily recognized cases of tuberculosis, so the disease is commonly referred to as bovine tuberculosis (bTB). *Mycobacterium bovis*, a member of the *Mycobacterium* tuberculosis complex, is the major causative organism of bTB (Inlamea *et al*., 2020).

Bovine tuberculosis in livestock is an infectious and chronic but disseminated disease. The disease recognised by the formation of typical granulomatous lesions, calcification, and encapsulation. BTB especially affects the respiratory system, so transmission and establishment of infection accrue mainly by route of the respiratory system (Menzies and Neill, 2000; LoBue *et al*., 2010). Another route of the transition of infection can occur via the gastro-intestinal tract. The infection can also become systemic and affect other body parts, such as the urinary tract or the mammary lymph nodes (Meng *et al*., 2009). Livestock farming bTB can directly disturb animal production and also impact the international trade of animal products.

By the time, a preferred method of bovine TB diagnosis is skin testing based on Single Intradermal Comparative Cervical Tuberculin (SICCT) test; accordingly, the positive cases would be sent to a slaughterhouse (Tadayon *et al*., 2013).

This test-and-slaughter is one of the policies controlling bovine tuberculosis that successfully condensed the prevalence of this disease in most developed countries (Cosivi *et al*., 1988; Tadayon *et al*., 2013). This is an integrated approach to food safety (Gordejo *et al*., 2006). However, the test-and-slaughter scheme is an expensive measure for the eradication of bTB from livestock populations in developing countries, and they are unable to apply it regularly (Torgerson *et al*., 2009; Michel *et al*., 2010).

The main risk factors contributing to difficulties in controlling bTB are production types, management activities, cattle movement, the existence of wildlife reservoirs, the existence of various strains, and possibly the survival of *M. bovis* (Carrique-Mas *et al*., 2008; Akbarein *et al*., 2014).

Cattle farming was recognized as an ancient activity in Iran (Tadayon *et al*., 2013). Several animal reservoirs were reported around the world, but the results of the few studies in Iran showed that the main source of bovine TB in cattle are present in rats (Akbarein *et al*., 2014), house mice, sheep, and goats, but buffalos are not normally infected with *M. bovis* in Iran (Tadayon *et al*., 2013). The law for the test-and-slaughter program was noticeably expanded from 1967 until 1977 for modern, semi-modern, and traditional cattle farms. In recent years, Iran has rapidly increased livestock production with improving production systems (Tadayon *et al*., 2013).

Iran has 31 provinces with a diverse range of climatic conditions. Among them, most parts of Razavi Khorasan province, located in the eastern half of the country, are deserts and arid lands, and somewhat mountainous areas. In these regions, cattle farmers usually purchase forage for their livestock from neighboring cities or countries such as Turkmenistan and Afghanistan. So, this practice impinges upon the spread of *M. bovis* strains. Epidemiological data on animal infectious diseases have been recorded daily by the implementation of the Geographical Information System (GIS), as a national surveillance system (Tadayon *et al*., 2013). To overcome the outbreak of these infectious diseases and the devastating economic burden, a fast alert system is needed in epidemic regions. To achieve this aim, some common approaches currently applied to forecast infectious disease morbidities; these include the linear regression method (Wang *et al*., 2006; Olsson *et al*., 2009), gray model method (Guo *et al*., 2008; Wu *et al*., 2008), artificial neural network method (Wu *et al*., 2006; Cunha *et al*., 2020), the Autoregressive Integrated Moving Average (ARIMA) method (Gharbi *et al*., 2011; Liu *et al*., 2011; Li *et al*., 2012; Wongkoon *et al*., 2012; Moosazadeh *et al*., 2014; Moosazadeh *et al*., 2015; Zheng *et al*., 2015; Esmaeilzadeh *et al*., 2020). ARIMA model consists of some subset models such as simple regression, multiple regression, and moving averages. It can represent the quantitative association between the objects during the time interval (Esmaeilzadeh *et al*., 2020). Hence, ARIMA model was applied to determine the temporal patterns of bTB cases between 2007 and 2018 in Razavi Khorasan province and to forecast bTB cases for one year later.

Materials and Methods

This cross-sectional study was conducted in Razavi Khorasan province, located in the northeast of Iran in the vicinity of Afghanistan and Turkmenistan. This province has an area of 112,769 square km and is divided into two mountainous and plain areas. In comparison with the other provinces, it has one of the most population of modern (European style) and semi-modern cattle farms (2,696 sites) in which the legislation of the test-and-slaughter program has been compulsory. The tuberculin Purified Protein Derivative (PPD) test is a chief method for bTB detection that classifies cattle to negative, inconclusive, or positive (reactor) and is recorded in a nation-wide GIS. Monthly accumulated data (reactor cases) is inquired from the Iran Veterinary Organization (IVO) from April 2007 until the end of March 2020. We used these data for a training model between April 2007 and March 2019 and for forecasting cases in the next coming year.

The ARIMA model was used for monthly reactor cases to remove the confounding effect of time. This linear model consists of three key parameters of p, d, and q where p indicates the auto-regressive (AR) part of the model. P incorporates the effect of lag value; d represents the number of non-seasonal differences needed for model stationary. The moving average (MA) was represented with q which is the number of lagged forecast errors in the prediction equation (Becketti *et al*., 2013; Esmaeilzadeh *et al*., 2020).

This analysis needs variance and means stationary data. We examined these assumptions by the Bartlett test for variance stationery, and the Augmented Dickey-Fuller (ADF) unit-root test for the mean stationery. The square root transformation was used for variance stationary but did not need the regular difference to remove the trend. We performed statistical methods on the transformed data. The autocorrelation functions (ACF) and partial autocorrelation functions (PACF) correlograms were plotted to estimate the number of autoregressive (p) and moving average parameters (q). Then, the Ljung-Box (Q) test was applied to evaluate the degree of fitness of the final selected models and considered the least value of the Akaike Information Criterion (AIC) to select the best-fitted model (Becketti *et al*., 2013; Esmaeilzadeh *et al*., 2020). Finally, root-mean-square error (RMSE) was calculated for the evaluation of the precise models. This was computed using equation 1:

$$\text{RMSE} = \sqrt{\frac{\sum_{t}^{N} = 1(\Upsilon_t - \gamma_t)^2}{N}}$$

Where,

Y_t: The observed monthly bTB

γ_t (gæmə): The predicted bTB at time t

N: The numbers of bTB (Esmaeilzadeh *et al*., 2019)

The statistical significance level was considered as $P \leq 0.05$. Stata (ver. 14) was used for statistical analysis.

Results

From April 2007 till March 2020, the annual average cattle herd size was about 18800 heads in Razavi Khorasan province. The PPD skin test was applied for

128000 heads, and 195 reactors were detected. The monthly average was 16.02 (±17.09) reactors.

The temporal pattern for training data (144 data points between April 2007 and March 2019) showed that the reactor numbers were more common in summer and autumn; however, there was no significant trend in these years (Fig. 1). The ARIMA model was applied to remove the confounding effect of the time. Meanwhile, the results of the Bartlett test revealed that the variances in this time series were heterogenous (P<0.001). So, we used the square root transformation on the data. The unit-root test on transformed data indicated that all the variable series were integrated series of order (P<0.001). We applied all statistical methods upon the square root of the data.

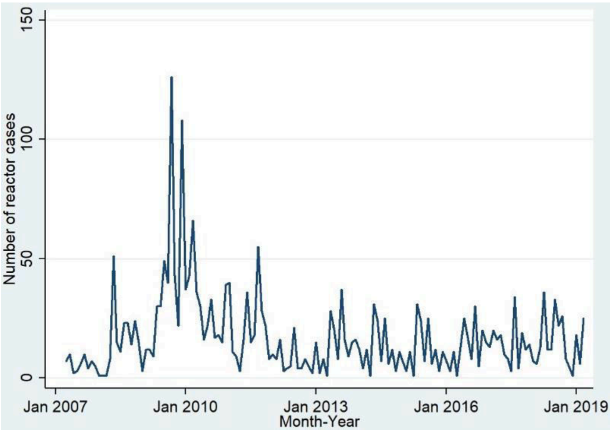

Fig. 1: The trend and distribution of bTB by month and year, between April 2007 and March 2019 in the northeast of Iran

Figure 2 showed that ACF and PACF represent the key parameters of the ARIMA model (p and q) more likely to be ≤3 (do not lie within 95% CI). Hence, this series was not a white-noise series (the variables in the white-noise series are independent and identically distributed with a mean of zero). These are the maximum chosen parameters, and we evaluated seven different models to find the best-fitted one. These models are indicated in Table 1. The residuals of all potential ARIMA models are white noise (P>0.05), so, all of these models can be suitable models. However, we performed the indicator of the optimistic model to choose the best-fitted one. Among these seven models, the optimistic model with suitable parameters was ARIMA (3, 0, 3) 12 based on the minimum of AIC (541.85).

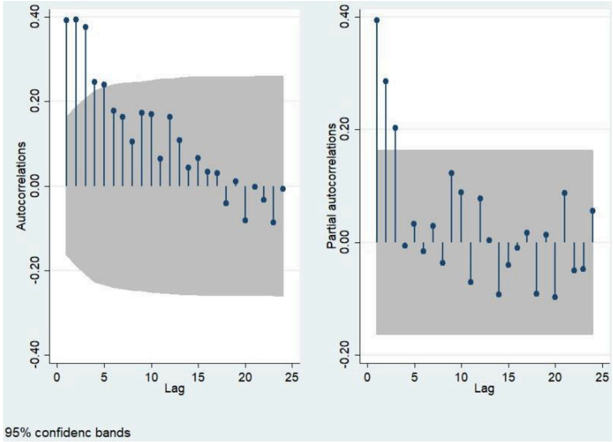

Fig. 2: Autocorrelation and partial autocorrelation plots on transformed data

In brief, the Wald test in the result of ARIMA (3, 0, 3) 12 regression represents that all six parameters are not zero; therefore, all variables are suitable predictors for the model (P<0.001). The coefficients of AR and constant (μ) are significant. The amount of "p" parameter indicates an increment in the PPT skin test at this time, leading to an increase of PPT skin test three months later. The coefficients of "q" parameter are not significant but improved the model, and d=0 indicates that these variable series were integrated series. The constant value (μ) has a high effect on the variability of the white noise distribution (Table 1).

Comparison of monthly observational cases and fitted model between April 2007 and March 2019 are represented in Fig. 3. The predicted bTB based on the best-fitted model cases followed an analogous pattern of observational bTB cases between April 2007 and March 2019. This model had a lower RMSE than other models (Table 1). This criterion indicates the high adequacy of this model for prediction in the future. The forecasted number and confidence interval of monthly bTB cases were 16.81[13.89-19.73], 13.84[10.84-16.84],

Table 1: Characteristics of ARIMA model's series of bTB between April 2007 and March 2019

Component	ARIMA (3,0,3)	ARIMA (3,0,2)	ARIMA (2,0,3)	ARIMA (2,0,2)	ARIMA (2,0,1)	ARIMA (1,0,2)	ARIMA (1,0,1)
Constant	3.71*	3.71*	3.70*	3.71*	3.70*	3.71*	3.69*
L1.AR	0.34*	-0.12	1.53	0.99	0.69*	0.82*	0.88*
L2.AR	-0.48*	0.52	-0.57	-0.15	0.13	-	-
L3.AR	0.79*	0.21	-	-	-	-	-
L1.MA	-0.10	0.35	-1.32	-0.77	-0.47*	-0.61*	-0.61*
L2.MA	0.74	-0.22	0.55	0.23	-	0.11	-
L3.MA	-0.55	-	-0.09	-	-	-	-
Ljung-Box (pv)	22.87 (0.98)	22.75 (0.98)	25.99 (0.95)	25.65 (0.96)	27.12 (0.93)	26.09 (0.95)	29.84 (0.87)
AIC	541.85	545.46	546.70	544.69	543.03	542.79	542.00
RMSE	1.50	1.53	1.53	1.53	1.53	1.53	1.54

AR: Autoregressive, MA: Moving average, L: Lag, Ljung-Box test: The portmanteau test for residuals white noise, AIC: Akaike information criteria, RMSE: The root mean square error, *: Sig., and -: Not applicable

12.69[9.53-15.84], 15.73[12.49-18.97], 15.05[11.79-18.31], 12.44[9.14-15.74], 14.21[10.85-17.57], 15.65[12.29- 19.01], 13.11[9.74-16.48], 13.02[9.62-16.42], 15.33[11.92-18.74], and 14.14[10.73-17.55] from April 2019 to March 2020, respectively. All values of the forecasted data were more than the observed cases. Therefore, these results are not concurrent with the results of the evaluated model (Fig. 3).

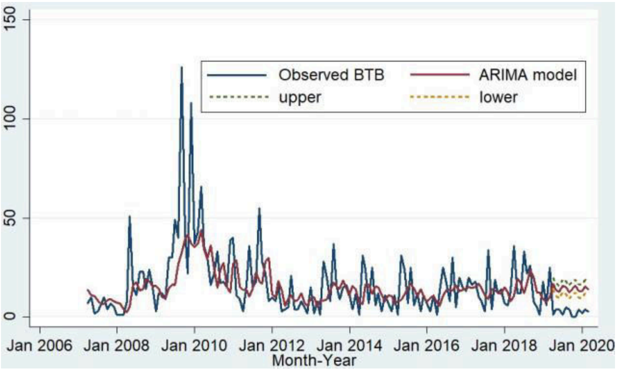

Fig. 3: The observed numbers, and the best ARIMA fitted models of bTB between April 2007 and March 2019 and the forecasted trend for one year ahead

Discussion

An analysis of surveillance data such as the ARIMA model on infectious diseases in a time series manner is essential to propose new hypotheses, forecast observed events, and then create a quality control system (Esmaeilzadeh *et al*., 2020). In recent years, Box-Jenkins models are used in medicine (Liu *et al*., 2011). However, these methods did not apply to infectious diseases in veterinarians. We studied the monthly reactors of bTB in the modern and semi-modern cattle farms in Razavi Khorasan province for the last 11 years. The findings of this investigation represent no clear pattern of change of bTB during this time. However, the fluctuation was observed in the record of the bTB positive test with one peak in 2009, with an increasing bTB number in summer and autumn. A fast-alerting system to predict the future in the epidemic region is required. This aim can be achieved using the ARIMA model. This model is one of the time series analyses. Some objectives of the time series analysis are removing a signal unknown in noisy data, excluding the cyclic and seasonal components from data, and simulating to forecast future values of the series (Brockwell *et al*., 2014).

This study indicated that the best ARIMA model for bTB in cattle is the non-seasonal ARIMA (3, 0, 3) model in Razavi Khorasan province. The zero in this model indicates that the mean of reactor cases did not show significant change over time. Between three lags of parameter p, the third lag has the most positive correlation with the current cases, so an increment in the current cases can lead to a 0.79 increase in the number of new cases three months later. A positive correlation exists between the current bTB cases and incidence case one month later (0.34), but an inverse correlation exists between the accrued infection at this time and the cases in two coming months (-0.48). The correlation between the current deviation and the deviation of one to three coming months are not significant (P>0.05), these differences can be due to some unknown factors. These monthly autocorrelations can be explained by the biological character of bovine tuberculosis. The incubation period of this infection has a wide range from months to years (Ciaravino *et al*., 2018), and these chronological orders are in an agreement with our findings. But the negative correlation can be discussed in relation to other factors that will be explained in the following.

The increasing number of cases in the summer and the autumn can be the result of the screening time schedules, transition of infection due to grazing animals in the spring, or accumulating them in enclosed places in winter. On the other hand, *M. tuberculosis* is the main agent of TB in human and can infect animals as well (Cosivi *et al*., 1998). *M. tuberculosis* in human, fascioliasis, and schistosomiasis can increase false-positive reactions to the PPT test (Claridge *et al*., 2012; Munyeme *et al*., 2012; Tadayon *et al*., 2013). *M. tuberculosis* in human has a seasonal pattern with the most incidence recorded in May in Iran (Moosazadeh *et al*., 2014; Moosazadeh *et al*., 2015; Esmaeilzadeh *et al*., 2019). The increased number of bTB in summer and autumn can be the result of human infection in spring. Although the ARIMA model was used, these cyclic pattern were not significant.

Another pitfall is the underestimating of bTB infection. The national test-and-slaughter program had significant effects on reducing the incidence of bTB, but only 10% of all susceptible herds (the modern and semi-modern cattle farms) are selected to be examined for bTB test and also farms in rural areas with poorer health measures have less access to veterinary services (Tadayon *et al*., 2013; Akbarein *et al*., 2014).

Time-series analysis attempts to solve these problems and consequently offers a good representation of the observed data (Brockwell *et al*., 2014). We predicted no change of bTB in recent years, however, the reduction of bTB cases was observed. This observed reduction can be the consequence of some exotic factors such as imposed serious trade sanctions, financial sanctions, and lost oil revenues (Abdollahzadeh *et al*., 2021), and natural disasters such as floods in the north-east of Razavi Khorasan province, and other provinces of Iran. These exotic factors likely reduce the sources of funding of health schemes including the test-and-slaughter program. Although the forecasted findings are not very precise, they are probably more accurate than the reported cases.

ARIMA is a linear function of past observational values and random shocks. This model is commonly haired for a short-term forecast (Esmaeilzadeh *et al*., 2020). Hence, the application and interpretation of ARIMA models are straightforward and can be considered as immediate tools for monitoring systems. ARIMA (3, 0, 3) 12 was introduced as a recommended fitted model to calculate numbers of bTB reactors in Razavi Khorasan province but the forecasted findings are not very precise. Therefore, we propose the Auto Regressive Integrated Moving Average with Exogenous Input (ARIMAX) model with some measurable exotic factors such as economic fluctuations, climate changes, and pulmonary tuberculosis in human to introduce a more precise and accurate model for the fast alert surveillance system. The finding of this study can help the local authorities and policy makers to enhance the health and well-being of the people living in the northeast of Iran.

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Conflict of interest

The authors declare that there is no conflict of interest.

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