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Human Brucellosis - New Public Health Problem in Bulgaria

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Abstract: The aim of this study was to describe trends over time of human brucellosis (HB) based on national surveillance data from 1992 to 2016 in Bulgaria and to assess the factors of its re-emergence after 50 years elimination. Retrospective analytical study was applied and performed descriptive, spatial and time series analyses using national aggregated data for HB incidence from National Center of Infectious and Parasitic Diseases (NCIPD)-Sofia. During the 25-year period, 190 confirmed cases were reported, resulting in annual incidence of 0.10 cases per 100,000 populations. Dynamic model of the epidemic process and risk factor were analyzed. The fitted Autoregressive integrated moving average (ARIMA) model of HB incidence also was selected. There were differentiated two cycles of infection spreading out lasting 12-13 years with two epidemic waves (1996 and 2002). Greater incidence of HB was recorded during the peaks of epidemic waves in the second epidemic cycle – 0.52-0.76/100,000 population. Re-emergence of brucellosis in Bulgaria started from areas bordering endemic countries and gradually extended inland. The geographic location of Bulgaria as external border of European Union (EU) and transit crossroad among Asia, Africa and Europe increases the risk of HB re-emergence to the country. Involvement of all responsible institutions for public healthcare is required.

Keywords: Human Brucellosis, Epidemiology, Public Health, Risk Factors, Bulgaria

1. Introduction

Brucellosis is one of the most widespread zoonotic diseases over the world. Brucellosis in humans is closely associated with occurrence and spread of *Brucella spp* in animals, particularly in farm animals. Currently, the brucellosis occurrence in a concrete country is based on epidemiology of disease in domestic animals. Recent data show, that endemic or potentially endemic are 179 countries. Globally, the prevalence of brucellosis varies widely due to new outbreaks, but it remains major health problem in developing areas of the Mediterranean region, Middle East, Western Asia and part of Africa and Latin America [1]. In endemic regions brucellosis is recognized to have an important impact on human and animal health, economic development, agricultural trade and even tourism.

Paleoepidemiology of brucellosis shows early signs of the existence of the disease in the Mediterranean basin. Mediterranean countries are recognized as primary endemic geographic region of human brucellosis (HB) [2, 3, 4]. Bulgaria borders with countries that maintain a continuous epizootic process such as Greece, Turkey and Macedonia. On the Balkan Peninsula, brucellosis is widespread in Albania, Bosnia and Herzegovina. Through the unfavorable geographical position in relation to brucellosis, a systematic disease control has been conducted in Bulgaria. Following the implementation of strict veterinary and border control measures about domestic animals and the generalization of milk pasteurization, ovine/caprine brucellosis has been eliminated in Bulgaria since 1941 and bovine brucellosis – since 1958. Since the first diagnosed case of HB in Bulgaria in 1903 to 90 years in the country are registered sporadic cases with a strong professional character. Political changes in the Balkan Peninsular since 1990 led to re-emerging of brucellosis in that geographic zone, including Bulgaria [5]. Due to re-designing of borders, the birth of novel countries, fundamental changes in the systems of public health and veterinary surveillance, free travelling of people, illegal animal trade and lost control of the borders had established an increased risk of infections, traditionally considered to be liquidated in Bulgaria.

The aim of this study was to describe trends over time of brucellosis based on national surveillance data from 1992 to 2016 in Bulgaria and to assess factors of its re-emergence after 50 years elimination.

2. Materials and Methods

2.1. Study Design

In the present study we retrospectively analyzed the annual time trends of morbidity of HB in Bulgaria during 25 years period (1992-2016). After 50 years period of elimination, a case of HB had been registered in 1992 on the territory of the country. We performed a research of time series data for HB to identify long-term trends and had established the country's dynamic model of the epidemic process of the infection.

The data from dynamic rows of brucellosis were investigated, using time series analyses. The results of epidemiological surveys of brucellosis on territory of the country, in order to establish the long term trends and describe dynamic model of epidemic process in the country were summarized.

2.2. Data Source

There were used national aggregated data for HB in Bulgaria from National Center of Infectious and Parasitic Diseases (NCIPD)-Sofia. The report of human cases must be accompanied by clinical signs and confirmed by serologic test; in accordance with the EU case definition for reporting to the Community network [6]. According to the Bulgarian procedures for registration of infectious diseases, all suspected and confirmed cases should be notified within 24 hours to the regional health inspectorate. After notification dedicated case questionnaire form submitted this to the national level using electronic surveillance system. The incidence rates (IR) was calculated per 100,000 of the total Bulgarian population [7].

2.3. Data Analysis

Descriptive statistics, spatial and time series analyses were performed with SPSS, v. 20 software and Microsoft Excel, 2010 v 4.00.

Time series analysis is one of the most powerful statistical tools applied in modern epidemiology of infectious diseases for describing, monitoring and predicting spatial and temporal variations in observed dynamic patterns. Autoregressive integrated moving average (ARIMA) models, also called Box-Jenkins models are increasingly used in infectious disease time series modeling. The actual values in ARIMA time series are based on the past values and past prediction error [8].

It was used TSMODEL Algorithms, Expert Modeler, SPSS, v.20 to specify an appropriate model of reemerging HB incidence rate in Bulgaria. TSMODEL procedure includes: building of univariative exponential smoothing, ARIMA, and transfer function (TF) models for time series, and produces forecasts. There was made tried to build custom non seasonal ARIMA model. The following parameters were selected to identify possible ARIMA (p, d, q) model: p (autoregressive order), d (degree of differencing), q (moving average order). There was also fixed automatic detection of outliers. The autocorrelation functions (ACF) and partial autocorrelation functions (PACF) of transformed series were used to estimate the values of p and q. The selected for diagnostics ARIMA models were checked with test statistics of the goodness-of-fit: normalized Bayesian information criterion (BIC), *R*-square (*R*2), Root Mean Square Error (RMSE), Mean Absolute Percentage Error (MAPE) and the Ljung – Box Q (18). The fitted ARIMA model was applied for short-term forecast of the annual incidence of HB in 2017 [9, 10].

All p values are 2-sided and statistical significance was set at $p \leq 0.05$.

3. Results

3.1. Reported Cases and Incidence Rates Per 100 000 of Human Brucellosis in Bulgaria 1992-2016

During the study period (1992-2016), a total of 190 confirmed HB cases were reported in Bulgaria, resulting in overall incidence rate of 0.10 cases per 100,000 populations (95% CI for mean 0.02-0.18). On Figure 1 is shown the curve of incidence.

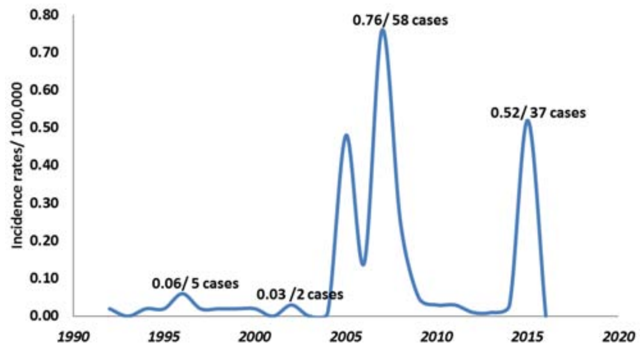


Figure 1. *Time series plot of human brucellosis, Bulgaria, incidence rates per 100,000 populations for period 1992-2016.*

Two cycles of infection spreading out were differentiated for surveyed period. The first cycle (1992-2003) includes the first case of brucellosis appearance in the country after 50 years of liquidation to 2003. Two outbreaks of the incidence – in 5-th year (0.06/100 000) and 11-th year (0.03/100 000) had been observed. There are five years between the epidemic periods. The epidemic waves have low intensity, with inclined ascending and descending curves, showing the small number of registered cases. In the second cycle (2004-2016) there were two epidemic waves – the first covering 2005-2009 with peak in 2007 (n = 58; 0.76/100 000) and second epidemic wave in 2015 (n = 37; 0.52/100 000). The epidemic waves are characterized by greater intensity sharply outlined ascending and descending lines of the curve with greater number of registered cases. Repeated five years period between the epidemic waves had been observed.

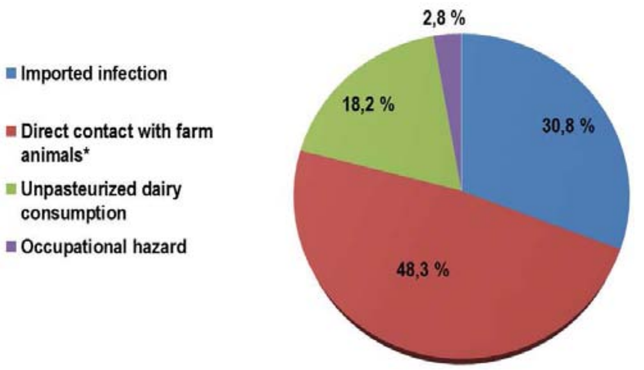


Figure 2. *Risks factor for human brucellosis (* - and consumption of non-pasteurized dairy products).*

Figure 2 shows then distribution of registered risk factors led to occurrence and spreading of the disease.

Half of inflicted 69 (48.3%) have been contaminated through direct contact with sick animals, predominantly goats and simultaneous consummation of non pasteurized milk products at direct contact with sick animals, 26 (18.2%) after consuming non pasteurized milk products, 44 (30.8%) imported infection - most frequently workers in Greek cattle-breeding farms, 4 (2.8%) with veterinary personnel in professional exposure.

3.2. Dynamic Model of the Epidemic Process

Trend and prediction of times series of HB were performed using ARIMA model. The raw data of HB incidence rates were transformed through a first-order differencing to provide the condition of stationary. The resulting ACF and the PACF plots were used to identify possible ARIMA process.

As shown in Figure 3 ACF and PACF start at lag 1 (r = -0.536; p = 0.005). The ACF tapering pattern to zero with slow decay in lag 1 PACF and considerably decay in lag 2 and lag 3 PACF suggesting AR (1) model or (p = 1). The ACF with a significant autocorrelation only at lag 1 is an indicator of a feasible moving average model (q = 1) or MA (1) model. We also included in different combinations probable parameters of AR (1, 2) and MA (0, 1) in order to build and select appropriate ARIMA model of HB incidence rates. The estimation of fitted ARIMA models was based on lower BIC and better MAPE. The ARIMA (1, 1, 1) model had the least normalized Bayesian Information Criterion (BIC) values of -7,147. The ARIMA (1, 1, 1) fit produced an R2 value of 0.992, normalized Bayesian Information Criterion (BIC) of -6,053 and maximum absolute error (MAE) of 0.018 (Figure 4).

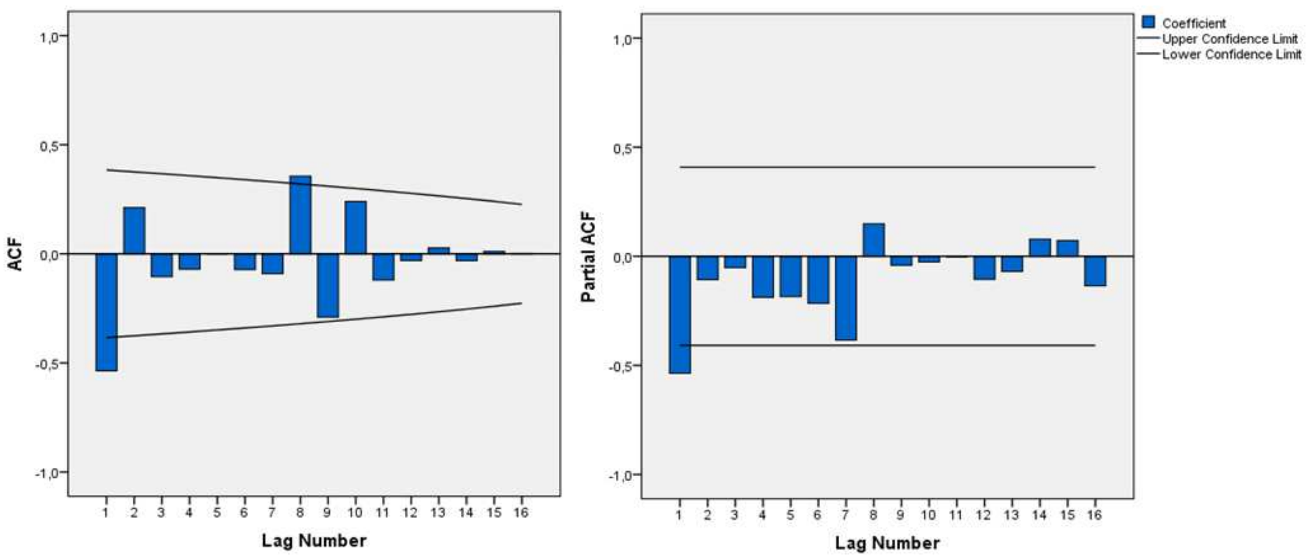
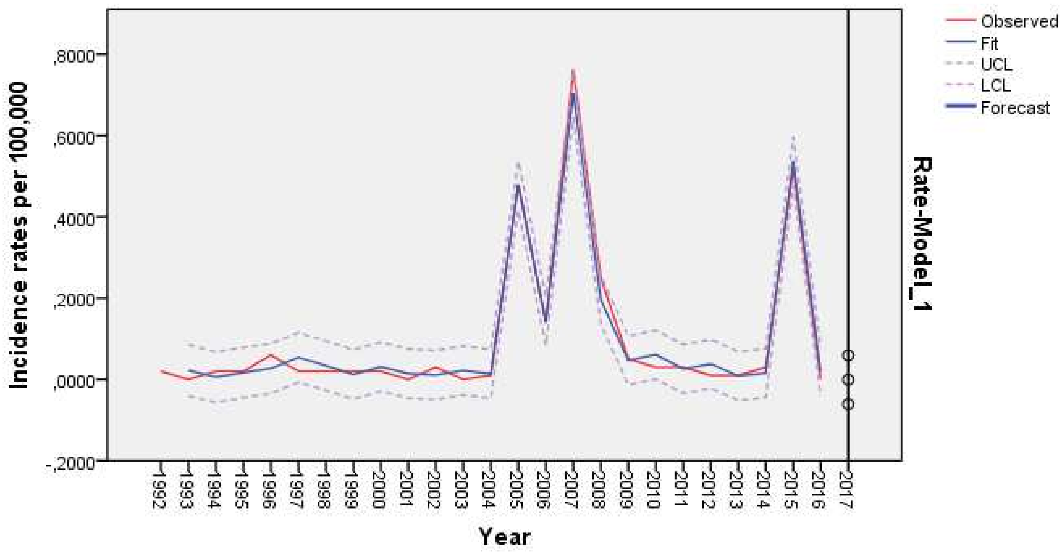


Figure 3. *Correlogram and partial correlogram - autocorrelation functions (ACF) and partial autocorrelation functions (PACF) after first order differences, human brucellosis incidence, Bulgaria, 1992-2016.*



*Underlined red lines indicate actual Brucellosis incidence, and red lines indicate fitting values predicted by (ARIMA 1, 1, 1) model

Figure 4. *Brucellosis incidence and fitting values predicted by ARIMA (1, 1, 1) model.*

The parameter of estimation of the optimal model also is shown in Table 1.

Table 1. *ARIMA (1, 1, 1) model parameters.*

Coefficients		**Estimates**	**S. E.**	**t-ratio**	**Sig.**
Constant		0.002	0.006	0.373	0.714
AR	Lag 1	-0.974	0.117	-8.342	0.0001
Difference		1			
MA	Lag 1	-0.901	0.275	-3.281	0.005

The goodness of fit test of the selected ARIMA (1, 1, 1) model showed non-significant autocorrelations in the residuals (Figure 5) - (Ljung-Box Q statistic = 14.5; p = 0.562).

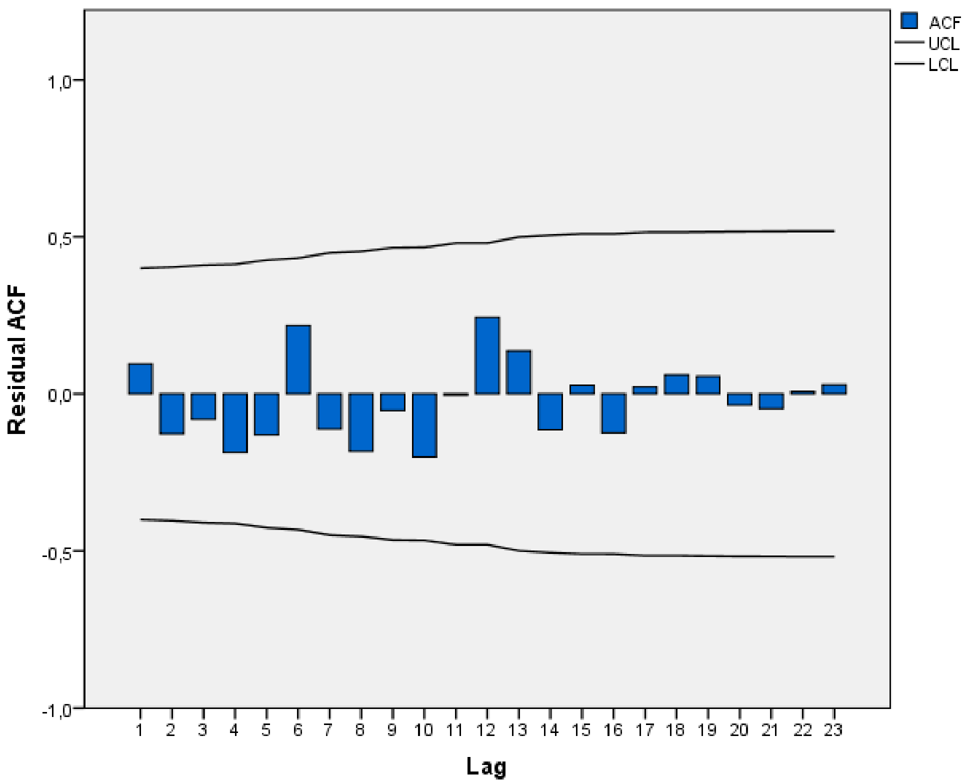


Figure 5. *Box plots of residual autocorrelations obtained from the ARIMA (1, 1, 1) model.*

The short forecast of annual incidence rates for 2017 produced from fit ARIMA (1, 1, 1) model were 0,0008 per 100,000 population with upper confidence level - 0.0593/100 000.

3.3. Status of Bulgarian Regions Regarding HB at the Time of Two Outbreaks - 2005-2008 and 2015

Since 1999, Bulgaria has been divided into 28 regions. Figure 6 presents the affected regions for the period 2005-2009 and 2015 year (incidence, morbidity, number of affected provinces). After re-emerging in Bulgaria, the cases of brucellosis initially cover border regions with Greece and Macedonia. Gradually other central areas of the country were affected. In 2005 there have been affected one border region and 3 central, respectively. In 2006 another 4 new regions were affected – 3 border and 1 in the country, in 2007 - 1 border and 1 in the country, and in 2008 were affected 3 central regions. In 2015 there were affected 4 new regions.

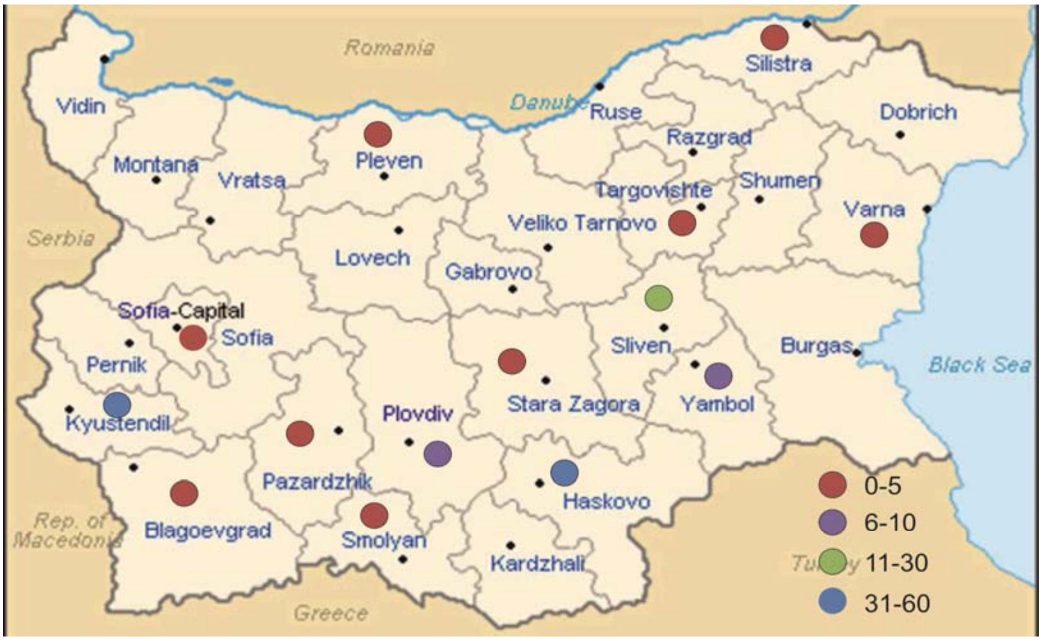


Figure 6. *Affected regions with human brucellosis (number of cases) for the period 2005-2015.*

4. Discussion

The analyses of the data in that survey established sustainable cyclic sequence in the spread out of HB in Bulgaria. Two epidemic cycles were observed with bimodal distribution of incidence. The cases in first cycle have not been profoundly investigated. They were sporadic, most probably related to import of infection from endemic areas, near neighboring countries. Despite the low frequency of HB cases during the first period 1992-2003, ARIMA prognosis model of epidemic process in 1992-2003 allows to significantly predict the first peak occurrence in 2007 and approximately the period of second peak occurrence during second period – 2004 to 2016. That fact suggests under estimation of the epidemic situation in first cycle, as well not notification of cases. We should note the fact that till 2003 animal brucellosis has not been registered.

In June 2006 during the second cycle of Smolyan region there have been recorded the first brucellosis outbreaks with goats and sheeps. In that region, the first case of HB has been registered, associated to animal infection in Bulgaria (7/11; 63.6%). In 2007 the second outbreak was registered in Haskovo, 53/58; 91.4% them directly related to epizootic process in Bulgaria [11]. The described by us second cycle terminated with second peak in 2015. An outbreak occurred in Rila town, Kyustendil region, and Rakita village, Pleven region (totally 37 cases, (100%) [12]. Over 88% of registered cases of HB occurred in second period (n = 158; 0.16/100 000). The incidence within peak periods of second epidemic cycle increased 12.7-14.3 times, compared to those of first epidemic cycle ($p < 0.02$). The relative share of registered cases of HB for period 2004-2016 had increased 1.6-2.2 compared to 1992-2003. The main risk factor in second cycle was direct contact with sick animals and/or consumption of non-pasteurized milk and milk products.

After accepting of Bulgaria in EU (2007) and providing free movement of goods and people, including animals and animal products, the risk of infection import in our country had been increased. Re-emerging of brucellosis in Bulgaria is related to the presence of brucellosis in Greece and Macedonia [13, 14]. Improvement of border control is required in order to prevent illegal import of animals as well increase the awareness of population in that regard with endemic areas [15, 16, 17]. The veterinary control and supervision should be increased, as well eradicate the tradition to consume non-pasteurized products in families of farmers. The usage of personnel protective equipment shall restrict the professional exposure of veterinary personnel [18, 19].

5. Conclusion

The geographic location of Bulgaria as external border of European Union and transit crossroad among Asia, Africa and Europe increases the risk of brucellosis re-emergence to the country. Involvement of all responsible institutions for public healthcare is required. The global epidemiology of human brucellosis during recent 15-20 years has considerably changed by socioeconomic factors, improved surveillance systems, animal-based control programs and international tourism.

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