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Epidemiology
Research Article

Epidemiological Forecasting of Crimean-Congo Haemorrhagic Fever in Bulgaria using the ARIMA Modelling Methods

Ani K. Kevorkyan[1], Ralitsa D. Raycheva[2], Radka T. Komitova[3] & Angel I. Kunchev[4]

[1] Department of Epidemiology and Disaster Medicine, Medical University of Plovdiv, Bulgaria; E-mail: ani_kevorkian@mail.bg
[2] Department of Social Medicine and Public Health, Medical University of Plovdiv, Bulgaria; E-mail: dirdriem@gmail.com
[3] Department of Infectious Diseases, Parasitology and Tropical Medicine, Medical University of Plovdiv, Bulgaria; E-mail: radkakomitova@yahoo.com
[4] Ministry of Health, Sofia, Bulgaria; E-mail: akunchev@abv.bg

Abstract: Crimean-Congo haemorrhagic fever (CCHF) is recognized as the most widespread tick-borne viral disease affecting humans. Bulgaria is the only European country where CCHF is endemic. However, the disease activity is also documented in the neighbouring countries. The period between the introduction of mandatory notification and registration in Bulgaria in 1953 till now covers 65 years and reflects the evolution of our knowledge of CCHF. For the study period (1953–2017) the average CCHF incidence in Bulgaria amounted to 0.29%ooo, decreasing from 0.49%ooo in 1953 to 0.03%ooo in 2017. The present study has shown stable CCHF incidence rates in the next 5 years using the ARIMA model for disease forecasting. Incidence forecasting is low and comparable to that of 2018. However, a new focus with territorial expansion ability has established in south-western Bulgaria, bordering North Greece. Further studies about the spread of virus in animals and ticks and early detection of human cases could provide the necessary data for risk assessment, preparedness and appropriate control measures.

Key words: Crimean-Congo hemorrhagic fever, incidence forecasting

Introduction

Crimean-Congo haemorrhagic fever (CCHF) is recognised as the most widespread tick-borne viral disease affecting humans (Al-Abri et al. 2017). The geographic distribution coincides with that of ixodid ticks, especially *Hyalomma* spp. (especially *H. marginatum*), which are the main competent vectors of the virus (Papa et al. 2017).The disease is endemic in Africa, the Middle East, western and south-central Asia and the Balkans, including Bulgaria (CCH Fever Final Report 2015). Crimean-Congo haemorrhagic fever is a significant public health concern because it has epidemic potential, a high fatality rate with no validated specific treatment or vaccine and a wide geographical distribution of the host tick reservoir.

The first cases of CCHF in Bulgaria were reported eight years after the disease was first recognized by M. Chumakov during the outbreak on Crimean Peninsula in 1944. Bulgaria is one of the countries with the highest traditions in studying the disease because a great number of cases were reported here and from the former Soviet Union as early as the first years after the virus was detected in 1967 (Appannanavar & Mishra 2011). The period between the introduction of mandatory notification and registration in Bulgaria in 1953 till now covers 65 years and reflects the evolution of our knowledge of CCHF. Furthermore, during the last two decades information is available about expansion of CCHF virus into neighbouring countries and geographically distant locations with cases among humans and virus detection in ticks and livestock (Spengler et al. 2019, Maltezou et al. 2010, ECDC 2009).

The purpose of the present study was to make epidemiological forecasting of CCHF incidence in Bulgaria over the period of 1953–2017 using ARIMA modelling methods, with a focus on some epidemiological characteristics of the disease over the last two decades.

Materials and Methods

Incidence data collection

The time series analysis was based on the official data for annual incidence (per 100,000 population) in Bulgaria for the last 65 years (1953–2017). The information was collected from six Bulgarian sources: the National Centre of Public Health and Analyses (NCPHA), the National Centre of Infectious and Parasitic Diseases (NCIPD), archive data in Annals of Bulgarian epidemiology (Annals of the Bulgarian Epidemiology in the Twentieth Century 2000) and the PhD theses by Vasilenko (1977) and Monev (1991) as well as the monograph by Radev et al. (1980).

Statistical analysis

We used the time series analysis to construct a time series model of the overall incidence (1953–2017) using the Time Series Modeller in SPSS v. 24. We established autoregressive integrated moving average (ARIMA) model for prediction (IBM SPSS Forecasting, IBM Corporation 2012, Somers, NY 10589). A p-value < 0.05 was considered statistically significant.

ARIMA Model

The ARIMA model was based on the yearly incidence CCHF rates (per 100,000 population, %ooo) from 1953 to 2017 in Bulgaria. We followed all three steps of the standard ARIMA methodology to establish the model: identification, parameter estimation, and diagnostic checking. First, we analysed the graphs for the autocorrelation function (ACF) and partial autocorrelation function (PACF) to identify the possible values of non-seasonal autoregressive order (p), non-seasonal differencing (d) and non-seasonal moving average order (q). Augmented Dickey-Fuller (ADF) test was used to determine whether the time series after differencing was stationary. In the second step, ARIMA model parameters were estimated. In the last step, we diagnosed the residual error sequence for white-noise sequence using the Ljung-Box Q test. Finally, we selected the best ARIMA model from the possible models based on the value of Bayesian Information Criterion (BIC), where the lowest BIC value showed the fitted model. For model evaluation purposes, data were split into three groups: training, validation and forecast. We built the time series model based on training group data (1953–2014), evaluation of the time series model (2015–2017) based on the validation group data and forecast the incidence rate for the next five years (2018–2022).

Additional epidemiological information about the territorial locations of the cases, including deceased during 1999–2018 was retrieved from NCIPD annual analysis. Cartographic method was used to visualise the data.

Results

For the study period (1953–2017), the average CCHF incidence in Bulgaria was 0.29 %ooo, decreasing from 0.49%ooo in 1953 to 0.03%ooo in 2017. The highest incidence index was recorded in two consecutive years, 1954 and 1955, being 2.75%ooo and 3.51%ooo, respectively. During the whole 65-year period, there were no years without registered cases. The annual number of cases varied from two (1994, 2007 и 2017) to 274 cases in 1955. The observed maximum was associated with the largest outbreak in 1954–1955, with a total of 487 cases occurring predominantly in NE Bulgaria, with both community-based and nosocomial patients. The CCHF incidence was not stationary for the period 1953–2014 (Fig. 1). The autocorrelation function faded rapidly after the first lag to values below zero for the 6th and the 7th lags and created a plateau after the 8th lag (Fig. 2) (see Brockwell & Davis 2002). As for the partial autocorrelation function, it had a high isolated peak at a delayed unit, then practically subsided below the confidence lim-

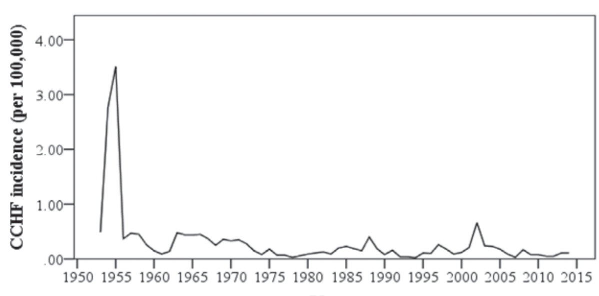

Fig. 1. Time series of the CCHF incidence rate for the period 1953–2014.

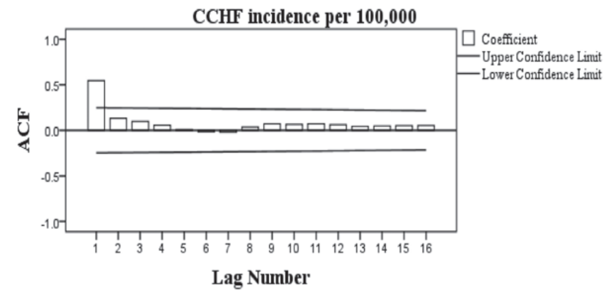

Fig. 2. Autocorrelation function (top) and partial autocorrelation function (below) of the CCHF incidence.

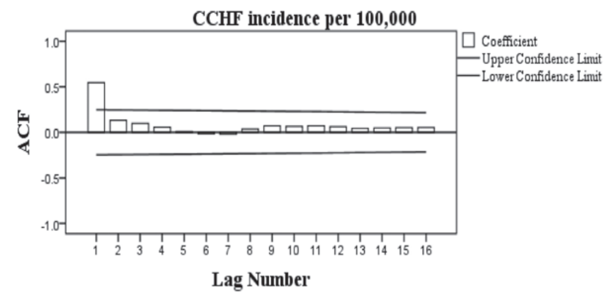

Fig. 3. CCHF incidence for the period 1953–2014 and its approximation performed by ARIMA (1,0,0) model.

Table 1. Time series, forecast and 95% CI intervals for CCHF incidence (validation data), 2015–2017.

Year		**2015**	**2016**	**2017**
Observed		0.06	0.06	0.03
ARIMA (1,0,0)	Forecast	0.12	0.12	0.12
	95% UCL	0.28	0.30	0.30
	95% LCL	-0.04	-0.06	-0.06

Table 2. Time series, forecast and 95% CI intervals for CCHF incidence (forecast) for the period 2018–2022.

Year		**2018**	**2019**	**2020**	**2021**	**2022**
ARIMA (1,0,0)	Forecast	0.05	0.07	0.08	0.10	0.11
	95% UCL	0.19	0.26	0.30	0.33	0.35
	95% LCL	-0.09	-0.12	-0.13	-0.14	-0.14

its (Fig. 2); such behaviour of the lengthwise samples indicates non-stationary series.

The "best fit" model was selected by using the Expert Modeller built in IBM SPSS Forecasting Analysis, which automatically identified and estimated the best fitting ARIMA. As a result, ARIMA model (1,0,0) was favoured. We have performed automatic outliers search that detected the existence of 5 outliers, as follows: 1954 additive: 2.34±0.08 (t=29.10, p=0.000); 1955 additive: 3.13±0.08 (t=39.25, p=0.000); 1974 level shift: -0.21±0.04 (t=5.38, p=0.000); 1988 innovational: 0.26±0.08 (t=3.26, p=0.002); 2002 additive: 0.46±0.07 (t=6.31±0.000). We modelled specific time points (1954 and 1955) as outliers because the extremely high incidence rate was a result of the above-mentioned largest outbreak in Bulgaria.

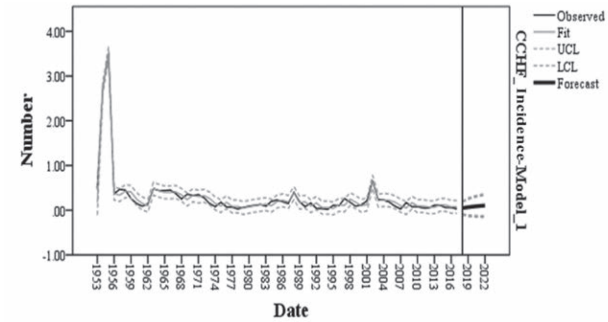

Fig. 4. Time series and ARIMA model (1,0,0) 5 years ahead CCHF incidence rates forecast.

The CCHF incidence in the period 1953–2014 and its approximation performed by the selected ARIMA model (Fig. 3) model provided a very good approximation to the CCHF time course and fitted the incidence dynamics. This one-step in-sample forecast demonstrated that the model was completely acceptable from a formal statistical point of view (R^2=0.96; Ljung-Box Q=10.16, p=0.897).

In the next step, we evaluated the ARIMA (1,0,0) model forecast accuracy over a period of 3 years (2015–2017, see Table 1). Finally, we demonstrated a forecast with a limited horizon outside the sample (2018–2022, see Fig. 4).

In addition to the epidemiological forecast of CCHF, we provided information about the territorial distribution of the CCHF virus infection cases, including those for 1999–2018 (Fig. 5). The data were related to the emergence of outbreaks of infections in the neighbouring countries. Two hundred and fifteen cases of CCHF virus infection were reported in Bulgaria between 1999 and 2018, with the fewest cases reported in 2017 (2 cases), and as many as 54 cases in 2002. Of these 215 cases, there were 45 with lethal outcome (fatality rate of 20.93%). Deaths were not reported in only four years (2010, 2011, 2016 and 2017). The fatality rate in 2015 was as high as 50%. The territorial distribution of patients (Fig. 5) showed that the most affected areas (the endemic areas) were six districts (out of a total of 28 districts in Bulgaria): Burgas, Haskovo, Yambol, Kardzhali and Sliven (all located in SE Bulgaria and sharing borders with one another) as well as the remote geographical area of Blagoevgrad. No cases of CCHF were reported from 12 districts (42.86%) in Bulgaria.

Fig. 5. Territorial distribution of CCHF (number of cases/number of deaths) notified in Bulgaria during the period 1999-2018.

Discussion

Bulgaria is the only country in the European Union where CCHF is endemic. However, the disease activity is also documented in the neighbouring countries (e.g. Albania, Kosovo, Russia, Turkey and Ukraine) (ECDC 2009, Health Protection Surveillance Centre Guidance Document 2018). The accumulated evidence in Bulgaria from observational, clinical and epidemiological studies (Vasilenko et al. 1970, Kovatcheva et al. 1997, Komitova et al. 2004, Monev et al. 2005, Kunchev & Kojouharova 2008) and modern molecular epidemiology allows a detailed analysis of the epidemiological process in terms of human cases (Papa et al. 2004, Kalvatchev & Christova 2008, Papa et al. 2016), animals (Barthel et al. 2014, Christova et al. 2018), vectors (Gergova et al. 2012, Panayotova et al. 2016) and serological prevalence (Christova et al. 2013, Gergova & Kamarinchev 2014) as well as the changes in the epidemiological dynamics and the geographical area of disease distribution in this country.

However, no studies on epidemiological forecasting of the incidence of CCHF have been carried out. The only study that comes close to the issue (Vescio et al. 2012) actually finds a correlation between CCHF incidence and selected environmental factors in 1997–2009 using the zero-inflated modelling approach. We have collected information about CCHF incidence in the period between 1953 and 2017 as a major intensive parameter, which enables us to make such an analysis. Historically, epidemiological forecasting is based on the complex biosocial nature of the epidemics studied over the years. Applying the conventional methods of descriptive and analytical epidemiology still does not allow a detailed analysis of the dynamics of the epidemiological process. Moreover, mathematical and statistical modelling methods have long remained underdeveloped and even underestimated in Bulgaria. Contrary to common practice, we have applied ARIMA model as available and scientifically validated forecasting approach that accurately short-term forecasts CCHF incidence. To the best of our knowledge, this is the first study in Bulgaria using the ARIMA model for incidence prediction. Three classical steps of the standard ARIMA methodology are used to build the model: identification, parameter estimation and diagnostic checking. In addition to the model evaluation purposes, data are split into three groups: training (based on data from 1953–2014), validation (based on data from 2015–2017) and forecast for the next five years (2018–2022). Based on the model statistics, we could assume that the ARIMA (1,0,0) model is accurate and provides a good fit for the epidemiological data set of CCHF incidence. We could also hypothesise that stable CCHF incidence rates up to 0.11 per 100,000 population are expected in the next five years (Table 2). The incidence of CCHF in Bulgaria for 2018 is 0.09‱o, which is in the range of our predicted ARIMA model.

For incidence prediction of infectious diseases, particularly CCHF, a variety of methods have been used by other authors such as Gaussian process regression (GPR) to make spatiotemporal prediction (Ak et al. 2018), a variant of ARIMA–SARIMA (Seasonal autoregressive integrated moving average) and Markov switching models (MSM) to examine the potential related factors of CCHF outbreaks (Ansari et al. 2015). Multifactorial logistic regression for temporal model design of the disease is also used (Mostafavi et al. 2014). Our study demonstrates that for the purposes of epidemiological control of the disease and related specific measures, the ARIMA model is an accessible and a high-precision short-term prediction model.

Some recent circumstances associated with the risk of outbreaks of CCHF deserve special attention. In 2006, the tick species *Hyalomma marginatum* has been detected for the first time on the territory of the Netherlands and South Germany (Al-Abri et al. 2017). The first autochthonous human cases were recorded in Greece in 2008 (Maltezou et al. 2009) and in Spain in 2016 (Negredo et al. 2017). Turkey has provided a special example of changing epidemiology of CCHF – after the first case of CCHF infection identified in 2002 (Karti et al. 2004), the country has transformed from free of human infections to an "epicentre" of the disease. Turkey has reported the highest number of cases in the world, with a total exceeding 10,000 (Leblebicioglu et al. 2016). All these data have reinforced the notion that the CCHF virus has a potential to expand and establish new endemic foci in Europe (Leblebicioglu et al. 2016). Due to the territorial proximity of Bulgaria to Greece and Turkey, we need to refine the data reported by the CCHF surveillance panel in Bulgaria by analysing in detail the cases of CCHF in each region of the country. Mapping the data obtained in the last two decades (Fig. 5) coincides with the time when cases of CCHF have emerged in the two neighbouring countries and shows a distributional pattern of infection concentrated in the eastern and southern regions of Bulgaria. This finding is consistent with the six focal areas reported in the late 1980s and early 1990s (ECDC 2009, Monev 1991). The data obtained by us show that there is a new focal area in a process of formation in Bulgaria, which is located in SW Bulgaria around the district of Blagoevgrad, which shares a border with Northern Greece. This district has reported the same number of cases as those recorded by the recognised foci of Haskovo, Kardzhali and Yambol. This new focus comes is the second one in the parameters of infection, after the oldest and active focal area until now in Bulgaria, the Burgas area.

The data from the latest outbreak of CCHF in Bulgaria, which occurred specifically in this area, corroborate the hypothesis that we are witnessing the formation of a new focal area in Bulgaria, which has the potential of expanding into other areas (Monev et al. 2005, Maltezou & Papa 2010). Two reports from the neighbouring northern Greece can additionally strengthen the possibility of a formation of a new focal area of the disease (Maltezou et al. 2010, Maltezou & Papa 2010). The first autochthonous case of CCHF infection in Greece has been recorded in 2008 exactly from territories adjacent to Bulgaria. The second case, an exported CCHF case from Bulgaria to Greece, was documented in 2018. A Greek construction worker got sick while working in the district of Blagoevgrad and later CCHF virus was isolated in Greece after his return (Christova et al. 2009). There are two further officially reported cases of CCHF infection exported from Bulgaria to other European countries: one exported into Germany in 2001 (Spengler et al. 2019) and into the UK in 2014 (Lumley et al. 2014). The latter case is related to the Burgas focal area of infection. Although the ARIMA model used in this study predicts a stable CCHF incidence in the country over the next five years, the comprehensive evaluation of the epidemiological process should also take into account several other factors indicating a spread of the CCHF virus infection. The evidence found in support of the increasing risk includes the high seroprevalence of CCHF virus in ruminants in areas with no human cases (Christova et al. 2018) and the presence of CCHF IgG antibodies in humans in two consecutive surveys. The survey conducted in 2001 has found seroprevalence of 2.8% for the country and 7.6% for Burgas area (Christova et al. 2013). Another survey in 2011–2012) recorded a seroprevalence of 3.2% (Gergova I. & Kamarinchev 2014). The last crucial indicator of the spread of this infection is provided by the two basic lineages of CCHF virus in Europe isolated from ticks in Bulgaria, i.e. the Europe 1 Lineage consisting of pathogenic strains and the Europe 2 Lineage containing AP92 and AP92-like strains isolated from *Rhipicephalus sanguineus* ticks from the region of Kardzhali, Bulgaria, for the first time (Panayotova et al. 2016). The CCHF virus of Europe 2 Lineage (AP92 and AP92-like strains) has been reported to have low or no pathogenicity causing only subclinical or mild infections in humans (Midilli et al. 2009). Such mild cases without haemorrhage have been observed in Kardzhali district in 2018 (Komitova et al. 2019), the same place where exactly AP92-like has been isolated from ticks (Panayotova et al. 2016). Further studies are needed to find possible correlation of the Europe 2 Lineage with the human disease.

In conclusion, the present study using the the ARIMA model has shown that stable CCHF incidence rates are expected in the next five years in Bulgaria. Incidence forecasting is low and comparable to that of 2018. However, a new focus with territorial expansion potential has been established in SW Bulgaria in an area bordering North Greece. Further studies on the spread of the virus and the early detection of human cases could provide the necessary data for the risk assessment and appropriate control measures.

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