Temporal analysis of visceral leishmaniasis between 2000 and 2019 in Ardabil Province, Iran: A time-series study using ARIMA model

Vahid Rahmanian[1], Saied Bokaie[1], Aliakbar Haghdoost[2], Mohsen Barooni[3]

[1]Department of Food Hygiene and Quality Control, Division of Epidemiology & Zoonoses, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran, [2]HIV/STI Surveillance Research Center, and WHO Collaborating Center for HIV Surveillance, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, [3]Department of Health Economics, Research Center for Social Determinants of Health, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran

Abstract

Background: Visceral leishmaniasis in human (VLH) also known as kala-azar is a neglected disease of humans that mainly occurs in more than 50 countries mostly located in the Eastern Mediterranean and the Northern America. **Objective:** The purpose of this study was to determine the temporal patterns and predict of occurrence of VL in Ardabil Province, in northwestern Iran using autoregressive integrated moving average (ARIMA) models. **Methods:** This descriptive study employed yearly and monthly data of 602 cases of VLH in the province between January 2000 to December 2019, which was provided by the leishmaniasis national surveillance system. The monthly occurrences case constructed the ARIMA model of time-series model. The insignificance of the correlation in the lags of 12, 24 and 36 months, and Chi-square test showed the occurrence of VLH does not have a seasonal pattern. Eleven potential ARIMA models were examined for VLH cases. Finally, the best model was selected with the lower Akaike Information Criteria (AIC) and Bayesian information criterion (BIC) value. Then, the selected model was used to forecast frequency of monthly occurrences case. The forecasting precision was estimated by mean absolute percentage error (MAPE). Data analysis was performed using Stata14 and its package time series analysis. **Results:** ARIMA (5, 0, 1) model with AIC (25.7) and BIC (43.35) was selected. The MAPE value was 26.89% and the portmanteau test for white noise was (Q = 23.02, $P = 0.98$) for the residuals of the selected model showed that the data were fully modelled. The total cumulative VLH cases in the next 24 months' in Ardabil province predicted 14 cases (95% CI: 4-54 case). **Conclusion:** The ARIMA (5, 0, 1) model can be a useful tool to predict VLH cases as early warning system and the results are helpful for policy makers and primary care physicians in the readiness of public health problems before the outbreak of the disease.

Keywords: Kala-azar, prediction, time series analysis, Iran

Address for correspondence: Dr. Saied Bokaie, Epidemiology and Zoonosis Division Department of Food Hygiene, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran. E-mail: sbokaie@ut.ac.ir

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Introduction

Visceral leishmaniasis in humans (VLH) or kala-azar is a zoonotic disease that is broadly spread in the world. The agents of this infection are L. *donovani* complex species. Two parasites containing *Leishmania donovani*and *L. infantum* caused VLH in the eastern hemisphere (old world) and *L. chagasi* in the western hemisphere (new world).[1-3]

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VLH is mainly reported from over 50 countries mostly located in the Eastern Mediterranean and the Northern America.[3]

Currently, VLH is an endemic disease in Iran and its prevalence is estimated at 2% in humans and 16% in the dog population.[2,4] In Iran, VLH is a Mediterranean type, and it is prevalent in some north-western and southern regions, with 100-300 new cases being reported every year.[1]

In Iran, dogs and canines such as foxes, jackals, and wolves are the main source of the disease.[4] Sandflies Phlebotomus Kandalaki and *Phlebotomus perfiliewi* in the northwest of the country, P. major in the central and southern regions of Iran, *P. keshishiani* and *P. alexandri* in the south of the country are vectors of VLH in Iran.[5]

According to the Ministry of Health and Medical Education of Iran (MOHME), 1,990 cases of VLH occurred in Iran between 2000 to 2019 and 30.25% of those cases occurred in Ardabil. Notwithstanding since 2008, the extensive public health activities have focused on prevention and control in surveillance systems; hence it was found that Ardabil had the highest cumulative incidence between 2010 and 2019.[6]

VLH is one of the diseases subject to mandatory reporting in the zoonotic disease surveillance system at the Center for Disease Control and Prevention of the Ministry of Health in Iran. In this system, demographic and clinical characteristics are completed in the form of epidemiological of definite cases of VLH in health centers or hospitals and then it is registered online in the surveillance system of this disease.

Establishing a surveillance system is essential for the rapid detection of leishmaniasis epidemics in animals and humans, as well as for the monitoring of possible epidemics. Also, the public health system, especially in endemic countries such as Iran, should be fully prepared to plan for epidemics. Therefore, it is necessary to use the models to predict the occurrence of leishmaniasis, especially in the areas with high incidence.

One of the most common models used in epidemiology is time series analysis, the most important purpose of which is to predict future values and the factors influencing their occurrence over time.[7] Different models are used in time series analysis when each has its own considerations and accuracy.[8,9]

In the recent years, some statistical models containing Autoregressive Integrated Moving Average (ARIMA) have been used to forecast infectious diseases such as brucellosis,[10] COVID-19,[11,12] influenza,[13] Crimean-Congo hemorrhagic fever,[14] and ZCL.[15,16] No studies have yet been performed in Iran to take into account forecasting VLH occurrence using time-series analysis. Thus, the objective of this study was to determine the temporal patterns of VLH occurrence from 2000 to 2019 in Ardabil province in northwestern Iran, and forecast the monthly occurrence of VLH between 2020 and 2021 in the province. The results of this study can be helpful for policy makers, local authorities and primary care physicians to adopt aggressive interventions for this infectious disease and implement clinical practice guidelines with the knowledge of predicting the occurrence of the disease in the future.

Materials and Methods

Study site

Ardabil province is located in northwestern Iran. The province had a population of 1,270,420 in 2016 (866,034 urban and 404,236 rural area) according to General Population and Housing Census. The ancient city of Ardabil is the center for Ardabil province. It also consists of 11 counties and has 2/3 mountainous textures with an average altitude of 3700 meters above the sea level. The city has four warm Mediterranean climates, temperate Mediterranean, cold, and temperate mountains. This city is known as the coldest regions of Iran and the province has between five to eight months of the cold year. Rainfall is also present in all seasons, but it is more intense in spring and autumn. Also, some tribes live in the northern and central districts.[17] Figure 1 shows the geographical location of Ardabil in Iran which is located in the northwest of the country.

Data

This descriptive study employed yearly and monthly data of 602 cases of VLH in Ardabil province between January 2000 to December 2019. The data were provided by the leishmaniasis national surveillance system at Ardabil University of Medical Sciences.

Furthermore, demographical information needed about these cases such as date diagnosis, age, sex, occupation, place of residence (city or rural), and nationality were extracted from this surveillance system.

Statistical analysis

ARIMA model

The monthly occurrences case during study period constructed the ARIMA model of time-series model. This model is described

Figure 1: Location of Ardabil Province in Iran

by three parameters including p: number of autoregressive (AR), d: number of times the model was differenced, and q: number of moving averages (MA). For estimation of the AR and MA parameters, autocorrelation functions (ACF), partial autocorrelation functions (PACF), and possible models were identified.[10]

In the next step, AIC lower (Akaike Information Criteria) and BIC (Bayesian information criterion) among possible models showed a better approach among models which were expanded by different lags.[18]

After that, the achieved ARIMA model was applied to predict frequency of monthly occurrences case. The forecasting precision was estimated by the Mean Absolute Percentage Error (MAPE), which was computed using the following equation:

$$MAPE = \frac{1}{N}\sum_{t=1}^{n}\frac{\text{Actual cases - Predicted cases}}{\text{Actual cases}}$$

where N is the number of prediction.

Analysis of data was performed using Stata software (version 14) and package time series analysis. To check the stationary in variance and mean, box cox regression and Dickey–Fuller tests were applied, respectively. To measure the goodness-of-fit of the final model, the portmanteau test for white noise and graphically checked the normality of the residuals. The alpha level was 0.05.

Results

Descriptive data

In total, 602 patients with a diagnosis of VLH were registered in the surveillance system, of which 53% were male and 47% were female. The median age of 3 years (IQR: 3.25) ranged from 6 months to 80 years were enrolled. The majority of patients (73.5%) were residence in the villages and 3% of patients had a previous family history of the disease. The most common clinical manifestations in patients were fever (100%), Anemia (78%), anorexia (71%), weight loss (58%), splenomegaly (47%), and hepatomegaly (14%).

Figure 2 shows that the trend of VLH cases between 2000 to 2020. According to this figure, the trend of this disease in the province has reduced significantly since 2005.

Since August 2010, there are reports of zero cases in some months of the year for smoothing and removing series noise, reducing fluctuations in the data and better presentation of series diagrams, as well as to eliminate the series regular and justified patterns of the moving average of order 3 method was used. This means that the average of the previous three data (in the previous three times) was replaced by each data, i.e., instead of the most recent data (xt), the average of the previous three data (i.e. xt-1, xt-2 and xt-3) was used [see Figure 3].

To evaluate the seasonal trend of VLH occurrence, Chi-square test was used (X2 = 5497.28, P = 0.411). This means that for the monthly data that is repeated every year, if it is seasonal, it is expected to report high cases of the disease in some months. The null hypothesis in this test is the absence of seasonal distribution of the disease. Furthermore, the trend was observed by plotting the line diagram, and this scheme shows no seasonal trend with a periodicity. Therefore, ARIMA model was selected for the fitting.

ARIMA model

The trend of monthly VLH cases in Ardabil province from January 2000 to December 2019 is shown in Figures 2 and 3. ARIMA model was created by the data of VLH cases during the study period. They displayed that the series were non-stationary in variances, and log transformation was used.

In the next step, to check the stationary in the mean the Autocorrelation Functions (ACF) and Partial Autocorrelation Functions (PACF) plots were drawn [Figures 4 and 5]. Considering these plots, it seems that there is no unstationary in the mean of the logarithm data obtained. On the

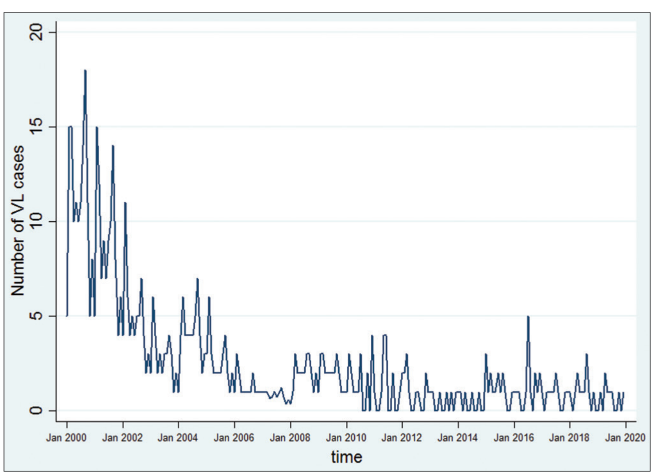

Figure 2: Trend and distribution 602 VLH cases between January 2000 to December 2019 in Ardabil Province

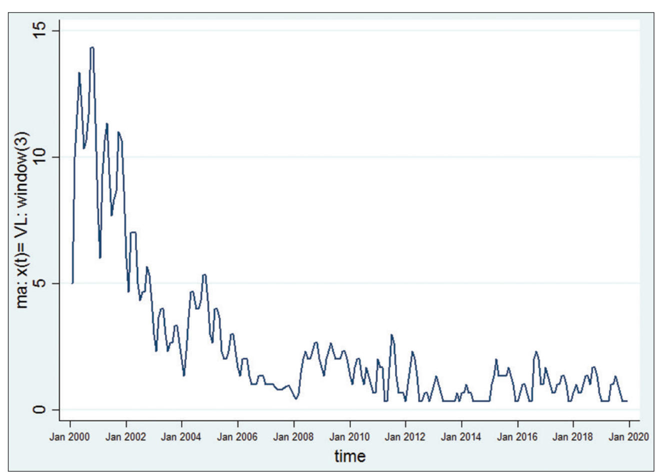

Figure 3: Smoothing trend and distribution of 602 VLH cases between January 2000 to December 2019 in Ardabil Province

other hand, Dickey–Fuller test showed that the data are stationary (P = 0.02).

Also, due to the non-sinusoidal wave of the coefficients and the insignificance of the correlation in the lags of 12, 24 and 36 months, it seems that the occurrence of VLH does not have a seasonal pattern.

To describe the main parameters of the ARIMA model (p, d, q), ACF and PACF plots were used. In these plots, the grey zone displays the 95% confidence interval and the lines that are continuously out of range are considered as significantly different [Figures 4 and 5].

The potential models for ARIMA for VLH cases were ARIMA (1, 0, 0); ARIMA (0, 0, 1); ARIMA (1, 0, 1); ARIMA (1, 0, 2), ARIMA (2, 0, 1), ARIMA (3, 0, 1), ARIMA (4, 0, 1), ARIMA (5, 0, 1), ARIMA (3, 0, 2), ARIMA (3, 0, 3), and ARIMA (3, 0, 4). Finally, ARIMA (5, 0, 1) was selected with the lower AIC (197.35) and BIC (225.17) for VLH cases.

For every potential model, time series analysis was performed. Then, by comparing the reduce and full models and calculating the likelihood ratio and the AIC and BIC quantities of the appropriate model is extracted and compared with each other.

Table 1 lists parameters of a ARIMA (5, 0, 1) model in which coefficients AR 1, 2, 4, 5 were statistically significant. The model's fitted cumulative number of VLH case from January 2000 to December 2019 are displayed in Figure 6. To evaluate the validity of the selected model, we showed the fitted model with actual data of VLH between January 2000 to December 2019, and then predicted the number of VLH cases from January 2020 to December 20201, based on the ARIMA (5, 0, 1) model. The predicted model is completely fitted to the actual data [see Figure 7].

The total cumulative VLH in the next 24 months' in the province was predicted 14 case (95% CI: 4–54 case) as summarized in Table 2.

To confirm the appropriateness of the model, the residuals (the difference between the actual cases and the predicted cases) were examined. The residual histogram showed that the residues follow the normal (Gaussian) distribution [see Figure 8]. The scatter plot of the residues [see Figure 9] confirms their independence and shows that the residual values do not have a specific trend and

Table 1: Coefficients and parameters of the ARIMA (5, 0 ,1) model to forecast the occurrence of VLH cases in the Ardabil province, Iran

Parameters	Coefficient	Standard error	95% confidence interval	*Z* statistics	*P*
AR (1)	1.87	0.14	1.59,2.15	13.10	<0.001
AR (2)	-1.15	0.18	-1.51,-0.80	-6.43	<0.001
AR (3)	0.06	0.12	-0.19,0.31	0.48	0.629
AR (4)	0.43	0.13	0.16,0.69	3.16	0.002
AR (5)	-0.21	0.09	-0.40,-0.02	-2.22	0.026
MA (1)	-0.84	0.13	-1.11,-0.58	-6.27	<0.001
Constant	0.58	0.99	-1.37,2.54	0.59	0.59
Sigma	0.35	0.01	0.32,0.37	28.13	<0.001

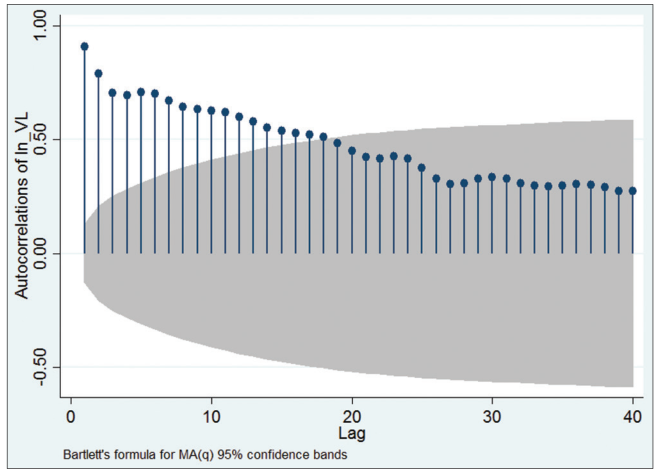

Figure 4: Autocorrelation functions (ACF) and correlogram plot of the trend in ln_VLH

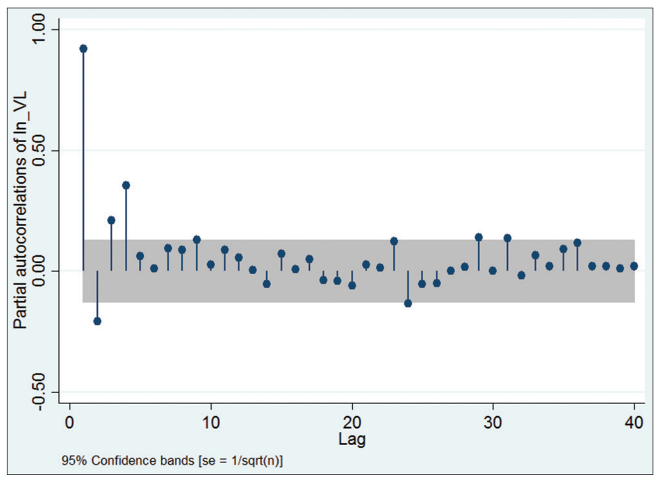

Figure 5: Partial autocorrelation functions (PACF) plots of the trend in in ln_VLH

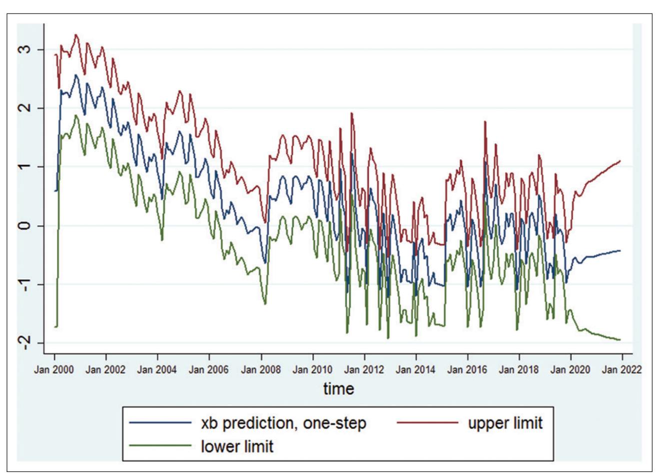

Figure 6: Model's fitted ln_VLH cases with 95% confidence interval between January 2000 to December 2021 in Ardabil Province

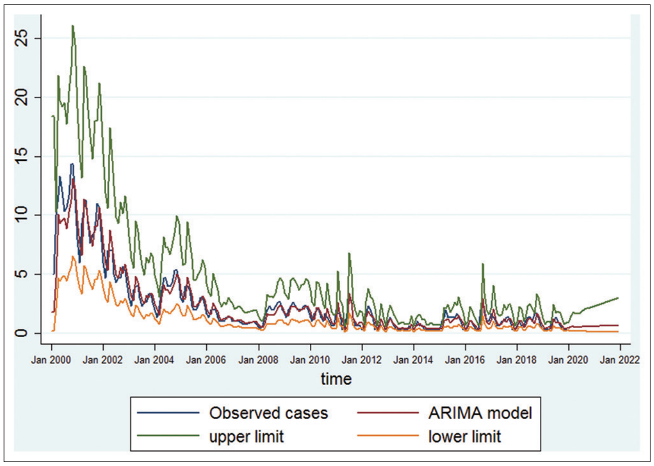

Figure 7: Observed VLH cases for the period between January 2000 to December 2019 and 1-step ahead predicted values between January 2020 to December 2021 based values on final selected ARIMA model

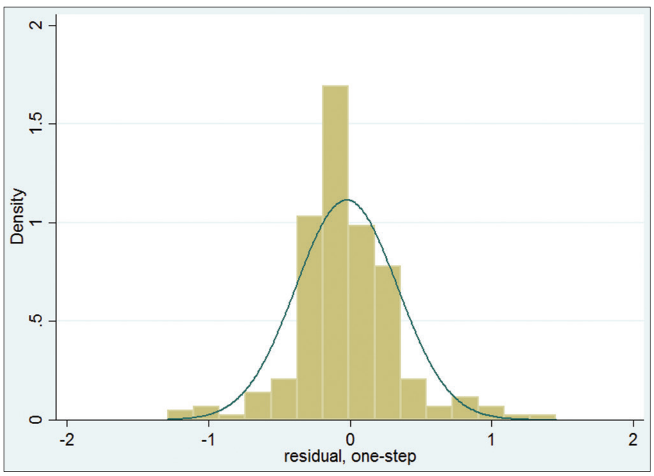

Figure 8: Histogram of the residuals in ARIMA (5, 0, 1) model

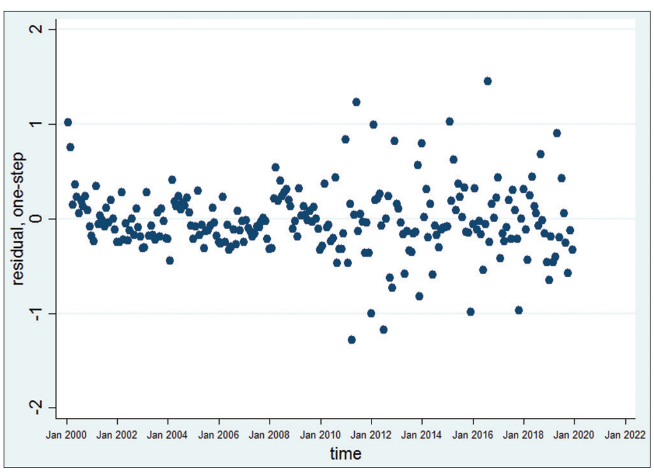

Figure 9: Scatter plot of the residuals in ARIMA (5, 0, 1) model

are randomly distributed. The mean absolute percentage error quantity was 26.89% and the portmanteau test for white noise was ($Q = 23.02$, $P = 0.98$) for the residuals of the selected model showed that the data were fully modelled.

Table 2: The forecast values (95% CI) according to fitted models of VLH cases for the period from January 2020 to December 2021

Events	Months	Forecast values	Lower values	Upper values
New cases	Jan 2020	0.47	0.24	0.94
	Feb 2020	0.56	0.21	1.50
	Mar 2020	0.59	0.19	1.80
	Apr 2020	0.54	0.17	1.70
	May 2020	0.52	0.17	1.65
	Jun 2020	0.53	0.17	1.70
	Jul 2020	0.56	0.17	1.86
	Aug 2020	0.59	0.17	2.02
	Sep 2020	0.59	0.17	2.10
	Oct 2020	0.59	0.16	2.13
	Nov 2020	0.59	0.16	2.16
	Dec 2020	0.59	0.16	2.22
	Jan 2021	0.60	0.16	2.30
	Feb 2021	0.61	0.16	2.38
	Mar 2021	0.61	0.15	2.45
	Apr 2021	0.62	0.15	2.51
	May 2021	0.62	0.15	2.56
	Jun 2021	0.63	0.15	2.63
	Jul 2021	0.63	0.15	2.69
	Aug 2021	0.64	0.15	2.76
	Sep 2021	0.64	0.15	2.83
	Oct 2021	0.65	0.14	2.89
	Nov 2021	0.65	0.14	2.96
	Dec 2021	0.66	0.14	3.02
	Total	14.28	3.92	53.78

Discussions

Time series analysis of surveillance data on infectious diseases is essential to stimulate new hypotheses, predict observed events and subsequently establish a quality control system.[19] In this study, we have introduced ARIMA (5, 0, 1) model as the ideal model to reflect the pattern of VLH occurrence in Ardabil province.

By looking into the AR parameters of the selected model, it displayed that the number of VLH cases in a given month can be predictable based on the number of cases of the disease in 1, 2, 4 and 5 months ago. Also, the deviation of the series data from the moving average from the time period 1 month ago is present in the model to predict the current time period.

Disease surveillance enables physicians, veterinarians, and those involved in human and animal health to diagnose an epidemic or the emergence of a new disease. Sometimes the decision to cluster disease or impossible events is simple, and the clusters are revealed simply by plotting the time series of events. However, under some circumstances, the clustering may be subtle and ambiguous. Furthermore, describing and comparing two, or more disease trends may be difficult based on visual interpretation of plotted time-series. In these cases, the statistical techniques may be helpful. The numerous techniques are existing for analyzing time-series data obtained from surveillance programs. It is a time series analysis method used in specific research situations in medicine and veterinary science to describe or forecast the temporal distribution of diseases.[20]

ARIMA model of time series analysis can be applied to predict VLH trends and supplement the common surveillance system to policy-makers and primary care physicians to prevent and control this infection.

This model can act as a tool to better understand the dynamics of VLH in a resource-constrained context with minimal data entry. This model also provides predictions that can be applied for planning in other infectious diseases in other areas.

The results of this study showed a prediction of decreasing incidence of VLH in Ardabil province in 2020 and 2021. The reductions in the incidence of VLH may be associated with disease control programs such as diagnosis, health education, knowledge and awareness of residents with the symptoms of the disease, destruction of disease reservoirs and spraying against vectors.

In the recent years, the use of ARIMA models in medicine and health, especially zoonotic diseases, has been increasing. Rahmanian *et al.* (2020) used the ARIMA (3, 0, 4) model to forecast human brocellosis in Yazd provine, Iran,[11] Tohidinik *et al.* (2018) applied SARIMA (2,0,0) (2,1,0,12) models to forecasting zoonotic cutaneous leishmaniasis in Fars provine, Iran.[15] Ansari *et al.* (2015) indicated SARIMA (1,0,1) (0,1,1,12) to forecast Crimean-Congo haemorrhagic fever incidence in Baluchestan, Iran.[14] Yang *et al.* (2015) used ARIMA (0, 2, 1) to predict incidence of Malta fever in China[9] and Esmaeilzadeh *et al.* (2020) used ARIMA (1, 0, 0), ARIMA (1, 0, 1), and ARIMA (1, 0, 1) for determining the new confirmed cases, the death cases, and the recovery cases of COVID-19 in Iran.[21]

This work is the first study to investigate and model the time series of visceral leishmaniasis. Most of the modeling performed on this disease has been spatial modeling[4-6,22] so far, but other studies in other countries of the world using different time series models such as scan statistics,[23,24] negative binomial regression,[25] Poisson[26] have modeled visceral leishmaniasis.

Time-series analysis is useful for describing long-series and cyclical periodic patterns and detecting atypical changes, but require lengthy observations typically well in excess of 50, and are unsuitable for new health surveillance.[20] Therefore, one of the strengths of this study is the entry of visceral leishmaniasis data for 240 months (20 years) in the model.

The limitations of this study are the use of existing data in the disease surveillance system and included secondary data. One of the inherent problems of secondary data is possible underreporting of all patients diagnosed in private and public hospitals.

Conclusion

The results of this study showed that ARIMA (5, 0, 1) model can be a useful tool for predicting VLHs in Ardabil province. Time-series models can be used as complementing national disease surveillance systems for early warning of the symptom. This can help policy makers and primary care physicians in the readiness of public health problems before the outbreak of the disease. Since infectious diseases fall into one of two stages, epidemic and non-epidemic, it seems that the use of mixed models (dynamic) in this case is superior to models that use a single distribution (static) for all observations. Therefore, we propose in future studies, other series models should be applied as they do not have this limitation.

Acknowledgement

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Ethical considerations

This research was approved by the faculty of Veterinary Medicine, University of Tehran, Tehran, Iran, (Ref: 7265130). In using raw data from the national leishmaniasis surveillance system, all principles were considered to protect the confidentiality of personal information of individuals.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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