

Basic Study

Modelling the prevalence of hepatitis C virus amongst blood donors in Libya: An investigation of providing a preventive strategy

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Abstract

AIM: To determine hepatitis C virus (HCV) seroprevalence among the Libyan population using blood donors and applying the autoregressive integrated moving average (ARIMA) model to predict future trends and formulate plans to minimize the burden of HCV infection.

METHODS: HCV positive cases were collected from 1008214 healthy blood donors over a 6-year period from 2008 to 2013. Data were used to construct the ARIMA model to forecast HCV seroprevalence among blood donors. The validity of the model was assessed using the mean absolute percentage error between the observed and fitted seroprevalence. The fitted ARIMA model

was used to forecast the incidence of HCV beyond the observed period for the year 2014 and further to 2055.

RESULTS: The overall prevalence of HCV among blood donors was 1.8%, varying over the study period from 1.7% to 2.5%, though no significant variation was found within each calendar year. The ARIMA model showed a non-significant auto-correlation of the residuals, and the prevalence was steady within the last 3 years as expressed by the goodness-of-fit test. The forecast incidence showed an increase in HCV seropositivity in 2014, ranging from 500 to 700 per 10000 population, with an overall prevalence of 2.3%-2.7%. This may be extended to 2055 with minimal periodical variation within each 6-year period.

CONCLUSION: The applied model was found to be valuable in evaluating the seroprevalence of HCV among blood donors, and highlighted the growing burden of such infection on the Libyan health care system. The model may help in formulating national policies to prevent increases in HCV infection and plan future strategies that target the consequences of the infection.

Key words: Autoregressive integrated moving average model; Libya; Hepatitis C virus; Blood donors

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Core tip: Hepatitis C virus (HCV) infection has major consequences and an overwhelming impact particularly among developing countries, hence prediction of its prevalence is important for future planning to mitigate its impact. This is an innovative study highlighting the importance of using a modified mathematical model to forecast and predict the future prevalence and consequence of HCV infection using data collected from blood donors. The results will allow strategists in health care services to plan immediate and long-term policies.

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INTRODUCTION

Hepatitis C virus (HCV) has been known to be one of the leading causes of chronic viral hepatitis with devastating consequences such as cirrhosis and hepatocellular carcinoma which are the major reasons for liver transplantation^[1]. The geo-epidemiology of HCV infection varies greatly and is dynamic over time^[2]. Indeed, 3% of the world's population are chronically infected with HCV and over 3 million new infection occur each year^[3]. Africa

and Asia represent the largest reservoir of chronic HCV infection^[4,5], though prevalence varies from one country to another and among regions within each country^[2,3]. The prevalence of HCV infection are highest in Africa, ranging from 1% to 26%, and Egypt, Senegal, and Cameroon have the highest rates worldwide^[6].

Hepatitis C is well documented in Libya and different studies have shown the prevalence of HCV infection and genotypes among Libyans^[7-9]. Recently a comprehensive study in over 1% of the Libyan population has shown that the prevalence of HCV infection is 1.2%, varying from 0.6% to 2.2% according to the region within the country^[10]. The prevalence indicated an alarming increase in HCV among the younger generation, particularly within new emerging risk groups in Libyan society such as intravenous drug users (IVDUs)^[10,11]. As age increases and disease progresses among infected individuals, there will be an increase in expected complications. This will place an increasing burden on the Libyan health care system which is still developing. Hence, studies should be directed to formulate policies to combat the effects of infection.

Early identification of epidemics of infectious diseases and prediction of their outcomes are an important step toward implementing effective intervention measurements and reducing mortality and morbidity^[12]. Such goals are a challenge in health care surveillance studies. Mathematical dynamic modeling has contributed greatly in exploring such challenges. Surveillance data however, are usually necessary for these modeling purposes^[13].

Different statistical models including linear regression and correlation coefficients have been used for prediction of viral hepatitis. Autoregressive integrated moving average (ARIMA) or Box-Jenkins has potential application in studies of disease dynamics^[14]. Helfinstein was the first to show that the ARIMA model can be used successfully for forecasting and predicting the different relationships between viral infections and associated diseases^[15]. Different studies applied such modeling to detect spikes, steps, and trends for hepatitis E, hepatitis B and hepatitis C infection^[16,17]. A considerable effort has been undertaken to forecast the epidemiology of hepatitis C, and different models were used to estimate the burden and complications of the infection^[18]. Recently, Corson *et al*^[19] used a mathematical model to project the future of HCV among IVDUs and its impact on the future development of HCV-related morbidity and mortality.

Blood donors are generally considered to be a healthier cohort of any community and viral hepatitis seropositivity among them may mirror the seroprevalence in the general population^[20]. In Libya, a study conducted between 1991 and 2001 indicated that the prevalence of HCV infection ranged from 1.2% to 1.6% among blood donors, similar to the prevalence among the general population reported in 2014 of 1.2%, though it was much higher (20.5%) among hospital personnel^[7,10]. Therefore, modeling and forecasting using HCV data from blood donors may provide an opportunity for planning

Table 1 Number of blood donors included in the study, Tripoli, Libya, 2008-2013

Study period	No. of volunteers	No. HCV seropositive
2008	35859	937
2009	65330	1713
2010	254177	3958
2011	173873	3060
2012	260139	4480
2013	218836	3749
Total	1008214	17897

2011-2013 were post-revolution years where many Libyan were injured during the Libyan conflict (2011)^[35]. HCV: Hepatitis C virus.

and intervention to control HCV infection. In this study, we aimed to forecast the prevalence of HCV trends among blood donors by analyzing HCV dynamics and highlighting the need for further intervention strategies.

MATERIALS AND METHODS

Ethical consideration

The study was reviewed by the Board of the Faculty of Medicine, Tripoli, Libya, who declared that the utilization and analysis of microbial epidemiological data did not require oversight by the Libyan National Ethics Committee. Hence, no ethical approval was needed for this study.

Study population

A total of 1008214 healthy individuals, aged 18 to 50 years, were recruited from three different main blood banks in Tripoli over 6 years from 2008-2013 (Table 1). These included Tripoli Central Hospital, Karda Teaching Hospital, and Tripoli Reference Laboratory. Each person was subjected to screening for known risk factors associated with blood donation according to the national and international standards applicable in all three hospitals. Those who failed to meet the criteria for blood donation were excluded from the study, such as those who had previous blood transfusion, jaundice, a history of illicit drug-taking, and other potential risk factors.

Laboratory diagnosis

The laboratory analysis was carried out using ELISA (Vitros EciQ, Orthodiagnostic-Switzerland), and samples were considered to be confirmed positive according to the manufacturer's instructions. HCV infection was defined as the presence of anti-HCV antibodies in the serum as detected by ELISA.

Modeling

The ARIMA model was developed to forecast the incidence of HCV infection among blood donors in Libya. This was applied using data for 72 mo between January 2008 and December 2013 to then forecast the incidence of HCV infection from January to December 2014 and predict the prevalence of HCV infection from 2008 to 2055 under nonexclusive expectation. The model was constructed

Table 2 Seroprevalence of hepatitis C virus among blood donors, Tripoli, Libya, 2008-2013

Yr	Prevalence (%)	OR	95%CI		Minimum	Maximum
			Lower	Upper		
2008	2.6	1.4	2.3	2.8	2.0	3.2
2009	2.6	1.4	1.7	3.4	1.1	4.1
2010	1.5	0.8	1.3	1.6	0.9	2.1
2011	1.7	0.7	1.3	2.0	0.8	2.8
2012	1.7	1.1	0.8	2.6	0.6	2.9
2013	1.7	1.1	0.9	2.5	0.7	2.7
Total	1.8	1.1	1.4	2.5	1.0	3.0

using the Box-Jenkins method. The identification and selection steps for ARIMA were carried *via* autocorrelation and partial autocorrelation functions. The model parameters were determined by the maximum likelihood method. Goodness-of-fit among ARIMA models was compared using diagnostic checks such as residual analysis and other relevant information. The accuracy of the model was finally subjected to critical estimation and rigorous checking to fulfill the required criteria for the model. The details of the ARIMA model were recently described by Yu *et al.*^[21] in 2013 and used to analyze the epidemiology of HIV infection among the Korean population.

Statistical analysis

Data were analyzed using Microsoft Excel, Minitab version 15 (State College, PA, United States), and SPSS version 16 (SPSS Inc., Chicago, IL, United States). A *P*-value < 0.05 indicated a significant difference between HCV and HBV prevalence. The Excel 2007 forecast function was used to predict the number of infected people. The following equation was used to calculate the expected number of infected persons each year, $1-Y = 613.2X + 836.5$, where *Y* = number of expected infected persons with HCV, and *X* = the serial number for the year calculated from 2008; for example for 2009 and 2010 the serial numbers were 2 and 3, respectively.

RESULTS

A total of 1008214 volunteer blood donors were screened for HCV over a 6-year period from 2008 till 2013. Of these, 17897 were found to be positive for anti-HCV antibodies, with an overall prevalence of 1.8%. There was no apparent monthly difference in HCV infection among individuals screened during the same year. Based on year-to-year analysis, a substantial variation in the seroprevalence of HCV was observed as shown in Table 2. The highest prevalence of HCV infection was reported in 2008 and 2009 as (2.6%) though it was 1.5% in 2010 and 1.7% in 2011-2013. In 2008, 35869 individuals were reviewed, of whom 937 (2.6%) were positive for anti-HCV antibodies. During 2009 the number of screened people doubled, and 1713 (2.6%) were positive for anti-HCV antibodies. In 2010, the number screened was 254177, a 7-fold increase compared with 2008, and 3958 (1.5%) were positive for HCV antibodies. In

2011, 3060 (1.7%) were HCV-positive. Although 260139 people were screened during 2012, the largest number over the 5-year period, the prevalence was the same (1.7%) as to that in 2011 and 2013, when a combined total of 218836 persons were screened (Table 1).

ARIMA modeling was applied to the data for identification, estimation, and then forecasting of HCV infection. The first stage was construction of an estimation model followed by forecasting and model evaluation. The data collected from 2008-2013 was used to construct the ARIMA model as depicted by Box *et al.*^[14]. Figure 1 shows the sample autocorrelation and partial autocorrelation functions [autocorrelation function (ACF) and partial ACF (PACF)] for the case structure which allowed identification of an appropriate ARIMA form to model the stationary series. A small variation was noted but it was not statistically different from zero which confirms the adequacy of the ARIMA model. The model forecast a steady increase for the following 6 years.

The sample ACF and PACF in Figure 2 showed a good fit which allowed us to determine the appropriate ARIMA model for HCV seroprevalence among blood donors. The adequacy of the model was evident as the residuals of autocorrelation had little variation with no significant difference ($P > 0.05$).

The plot of observed vs fitted values indicated that the model provided an excellent fit of the data as shown in Figure 3. The ARIMA model was used to forecast HCV prevalence for 72 mo over the 6-year period from January 2008 to December 2013 (Figure 3). Detailed analysis of observed vs forecast values of HCV prevalence over the study period showed a steady increase, with a maximum value at 1.8% to 2.01%, and an increasing tendency beyond the observed period in the short-term forecast (January-December 2014), reaching a maximum of 700 per 10000 population (2.3% to 2.7%). This was then used as a basis for estimating the prevalence of HCV infection among the Libyan population up to 2055, based on 6-year periods (Figure 4). According to our model, the prevalence of HCV infection will decrease and thus all sequelae of the infection will continue to decrease steadily in the future.

DISCUSSION

HCV infection has been known to be an important cause of chronic liver diseases though accurate representative epidemiological data are difficult to obtain, particularly in developing countries, as this infection has been considered to be endemic^[2]. Statistical analysis of surveillance data on the prevalence of various infections was shown to be helpful in establishing a hypotheses to highlight and anticipate the dynamics of HCV infection and subsequently implement appropriate preventive measures and allocation of required resources^[22]. The ARIMA model is one of the most widely used forecasting techniques due to its structured modeling base and acceptable forecasting performance^[23].

In this study, we developed a calibrated ARIMA model for HCV infection with the aim of taking full advantage

of available epidemiological information from registered blood donors in Libyan blood banks. The overall prevalence of HCV among the blood donors was found to be 1.8%, ranging from 2.5% in 2008 to 1.7% in 2013. This is consistent with a recent comprehensive study published by our group who reported that the prevalence of HCV among the Libyan population varied from 0.6% to 2.2%^[10]. Comparing such results with regional published data, the prevalence of HCV infection was found to be similar to that in neighboring countries, with 1.6% in Tunis and 1.8% in Algeria, though it was higher in Egypt (22%)^[24,25]. However, this was higher than the prevalence among developed countries such as the United States and Germany ($< 1.5%$)^[26,27]. Hence, further studies are needed to elucidate the different factors associated with the higher prevalence of HCV among Libyan blood donors.

In our study, the applied model showed accuracy for the prevalence and dynamics of HCV infection among blood donors over a 6-year period and the forecast after that. This is in agreement with other studies who also declared that this model provides a better forecast than traditional methods for case notification of an infectious disease^[28]. Although the prevalence of HCV was steady over the last 3 years (1.7% for 2011-2013), we predicted an increase for the year after. This was consistent with other studies from China and Latin America which showed that the prevalence of HCV was steady or increasing and that the number of infected individuals will increase^[29,30]. This suggested that other risk factors are set to play a major role in continued new infection. Further studies are needed to clarify such an assumption.

Despite the increase in rates of HCV seropositivity in this study, we did not predict the burden of HCV infection over the next decades, nor did we calculate the estimated number of individual morbidities associated with HCV infection. However, different studies have shown that the prevalence of HCV-related cirrhosis is expected to increase by 24% within a decade, though decompensated cirrhosis cases and hepatocellular carcinoma will increase by 50% within the same period^[31-33]. Hence, further studies are needed to elucidate such consequent complications of HCV infection among Libyan populations.

Modeling studies have projected a dismal future for HCV infection and related disease burden. In general, these models make forecasts based on current conditions of low rates of screening and treatment, and thus do not include a widespread program of identifying and treating the large proportion of undiagnosed HCV-infected individuals^[34]. According to the results of our model, the incidence of the more serious outcomes of HCV infection will continue to rise, at least until 2055, unless modified. In our projections of HCV infection to 2055, we did not take into account the effective HCV prevention programs and the possible impact of the use of antiviral medications. Both these developments could have a considerable impact on our future projections, and thus the prevalence of HCV infection projected to 2055 may be less than that estimated by our model. Furthermore,

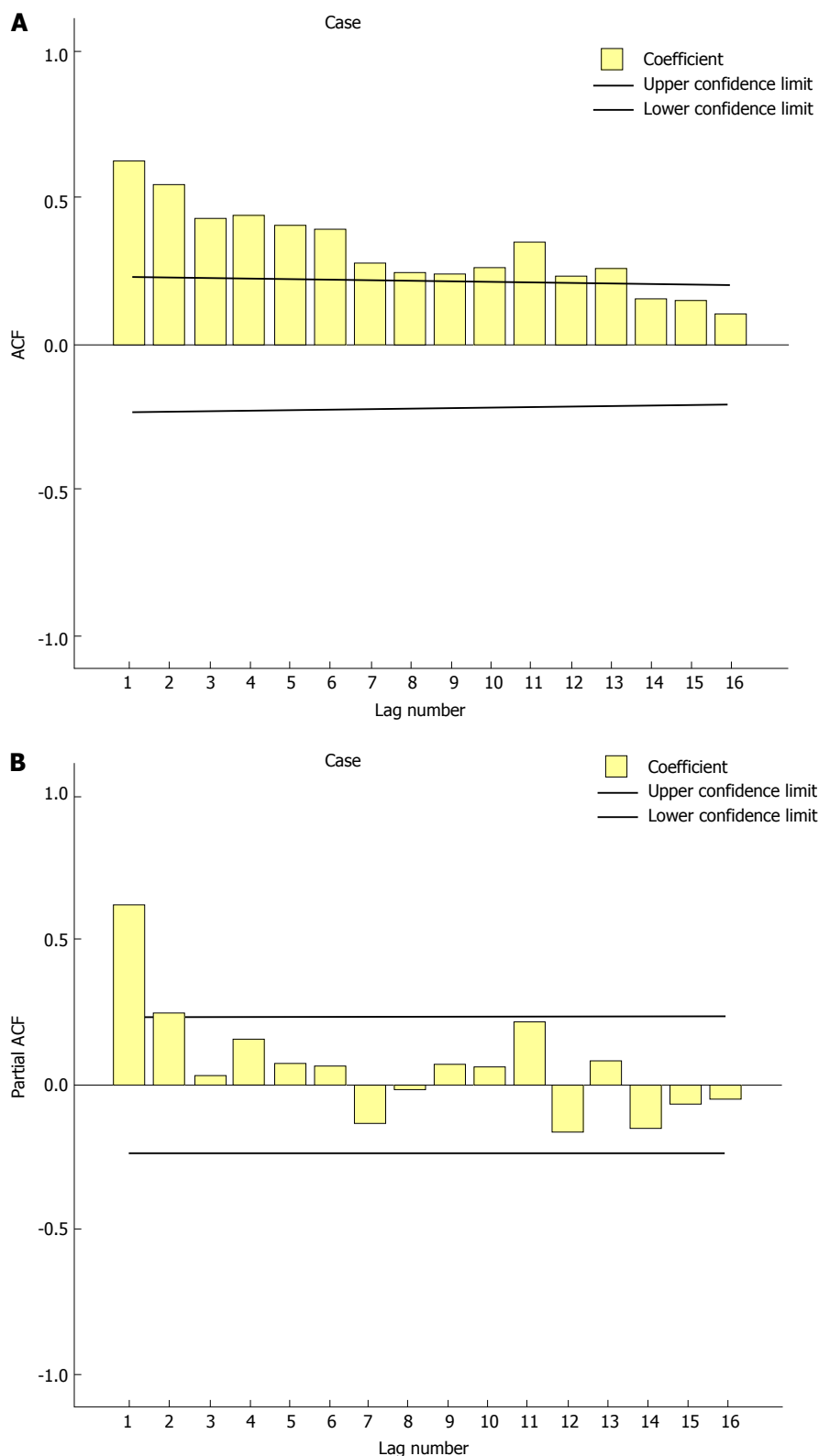


Figure 1 Correlogram and partial correlogram for a case structure control used for autoregressive integrated moving average model. A: ACF; B: Partial ACF. ACF: Autocorrelation function.

socioeconomic conditions in the country should be taken in consideration, particularly among developing countries; Libya is experiencing a major challenge regarding its geographical, political and social-ethnic identity^[35,36]. Thus, future planning regarding infectious disease should

be prioritized^[37,38].

Monitoring HCV seropositivity among blood donors could be used to evaluate the effectiveness of the national efforts and guidelines to provide safe blood donation and good blood bank services^[39]. In many

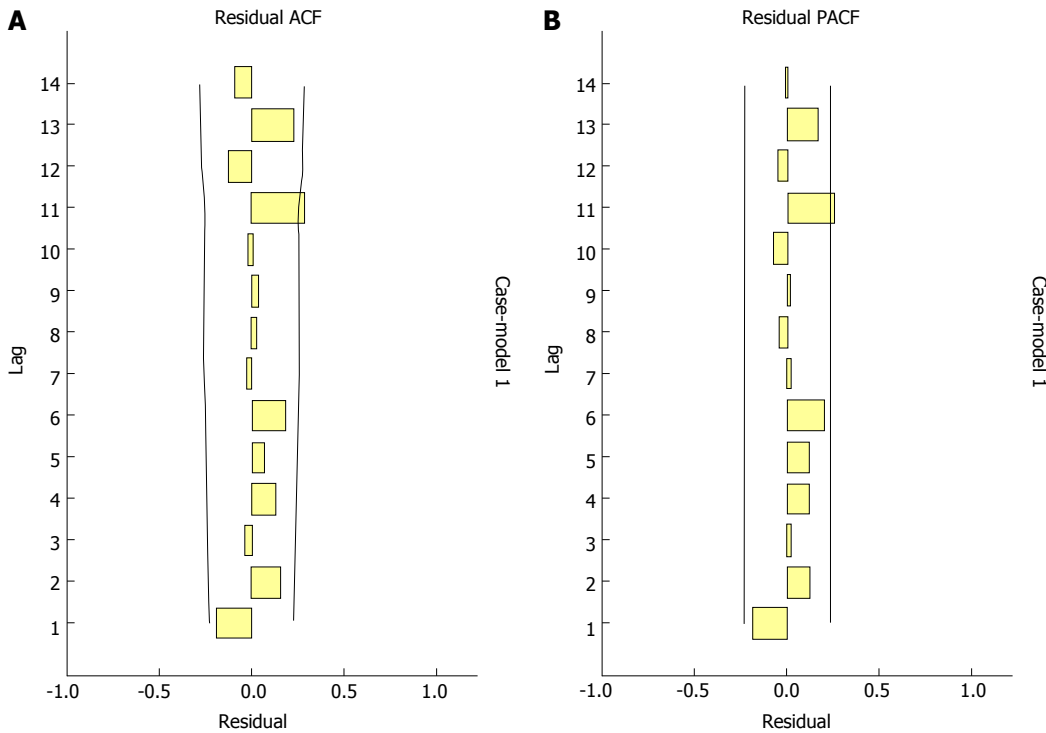


Figure 2 Residual plots for the final autoregressive integrated moving average (2, 1, 7) model of hepatitis C virus seroprevalence among volunteer blood donors in Libya, 2008-2013. A: ACF; B: Partial ACF. Lines indicate 95%CI. ACF: Autocorrelation function.

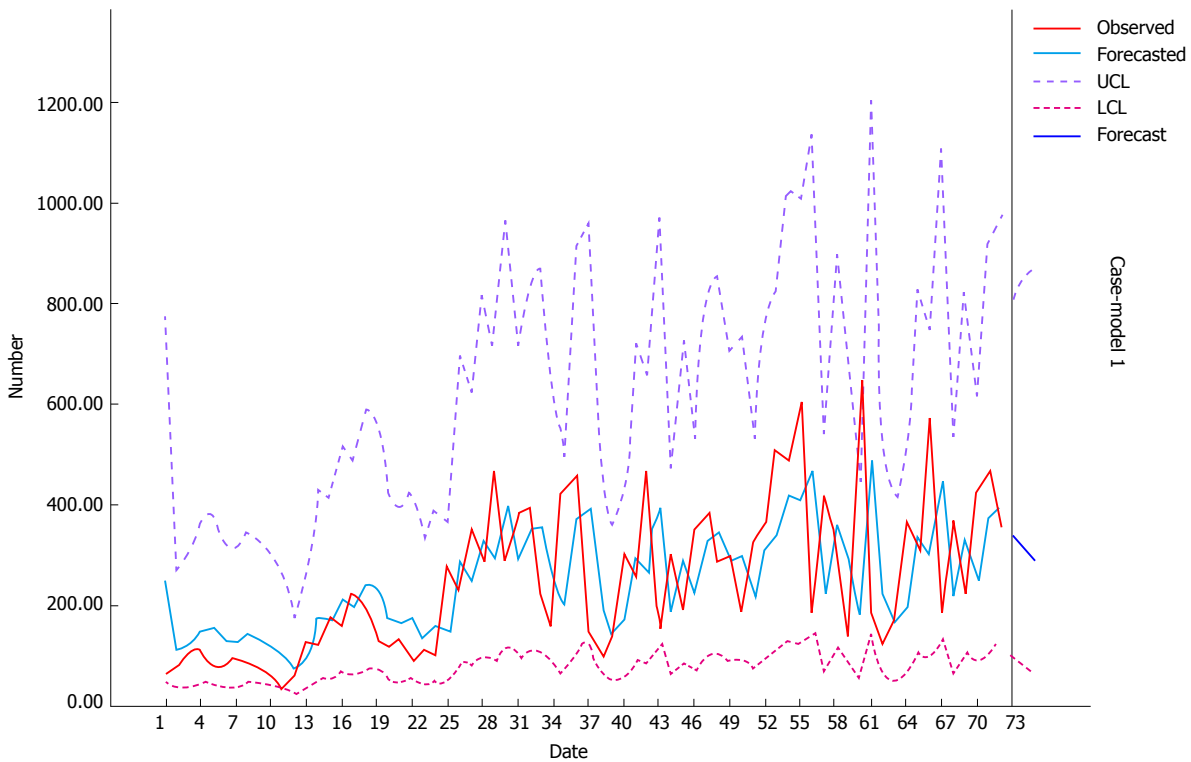


Figure 3 Number of observed and forecast hepatitis C virus seropositive volunteers among blood donors in Libya, 2008-2013. Date: Period of observation (months: 2008-2013); Number: Estimated number of HCV seropositive/month. UCL: Upper confidence limit; LCL: Lower confidence limit; HCV: Hepatitis C virus.

countries, HCV transmission rates decreased markedly with the introduction of blood screening^[40]. Despite such a decline, mathematical models still predict a continuing rise in the prevalence of HCV infection within

blood banks^[41]. This was evident in our study where the increase in HCV seroprevalence may be attributed to the lack of quality assurance within the blood donation system. In Arab countries, blood transfusion is still a

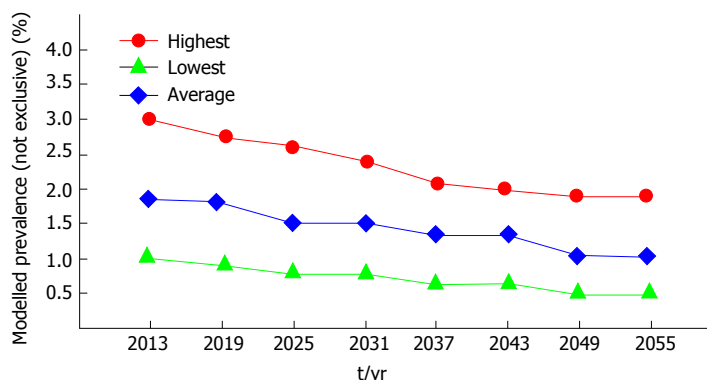


Figure 4 Modeled prevalence (not exclusive¹) of hepatitis C virus infection by 6-year period, Libya, 2008-2055. ¹Estimates assume stable risk populations and HCV infection risks and do not adjust for treatment. HCV: Hepatitis C virus.

problem due to lack of an organized infrastructure and altruistic volunteers. The main sources of blood donation are usually relatives and friends who attend because of social pressure and in an emergency where questions regarding risk behaviors are rarely asked^[2].

Many difficulties surround the determination of HCV prevalence using blood donors, since high risk groups including IVDUs are often excluded from blood donation, leading to underestimation of the true prevalence of HCV infection^[42]. Nevertheless, our data do not necessarily represent the true HCV prevalence among the general population and thus are in need of further updating. The applicability and effectiveness of this monitoring system in its practical application as conducted here is able to detect the epidemic situation of HCV infection in Libya. However, such an infection is dynamic and evolves over time. Therefore, the model should be periodically reassessed and updated to maintain long-term sustainability and precision. This study highlights the need for preventive initiatives and strategies to be adapted by health care policy-makers to reduce HCV infection.

In conclusion, there is an important need for monitoring and predicting the prevalence of HCV infection to reduce the substantial consequences particularly in developing countries. The model applied was verified and could be used to monitor and predict the epidemiology of HCV infection. A better understanding of the epidemiology of HCV infection will allow health authorities to revise and plan new strategies within the health care system.

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COMMENTS

Background

Viral hepatitis, particularly hepatitis C virus (HCV) is known to be a serious

problem particularly among developing countries. Hence, using a simple and reliable method for predicting the future course and consequences of this infection are a priority for researchers and health care planners. Reliable data regarding the prevalence of HCV infection among blood donors are available in all blood banks and this could be used to achieve such objectives.

Research frontiers

Studies on the prevalence of HCV infection utilizing blood bank data could be used as a basis for future planning. However, such studies are rare and few researchers have focused on using such data as a model for future planning.

Innovations and breakthroughs

This is a novel study which applied a mathematical model utilizing basic data from blood banks regarding the pathogen HCV. This is a rare study which modeled data to predict the prevalence of HCV infection among the general population over the next 50 years (2008-2055).

Applications

The practical approach of this study allows strategists and health care professionals to plan appropriate intervention and prevention methods not only to minimize the spread of HCV infection but also to reduce the associated consequences and complications, such as hepatocellular carcinoma and cirrhosis, and may be used further for other infections such as hepatitis B virus and human immunodeficiency virus.

Terminology

The ARIMA model is an autoregressive integrated moving average or Box-jenkins mathematical model which has a potential application in studying disease dynamics. The model can be used successfully for forecasting and predicting the relationships among viral infections and associated diseases.

Peer-review

This is a well conducted epidemiologic study carried out in a developing country.

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