Abstract

Background: The World Health Organization (WHO) has aimed for a 30% reduction in hepatitis B (HBV) and hepatitis C (HCV) incidence by 2020. To achieve this goal, it is important to have updated information about trends in the hepatitis incidence rate. However, there is a lack of up-to-date data from East Azerbaijan province in the Islamic Republic of Iran.

Aims: This study aimed to estimate the HBV and HCV incidence rate from 2011 to 2016 in East Azerbaijan, Islamic Republic of Iran.

Methods: Hepatitis data and population data were obtained respectively from the national notifiable disease surveillance system and the national Iranian census for 2016. For quantifying the rate of changes in incidence rate from baseline, the average annual rate of reduction (AARR) was calculated. For this, the linear regression model was used for estimating the beta coefficient. SPSS V25 was used for statistical analysis.

Results: Over the 6-year period, 3119 hepatitis cases in East Azerbaijan province were reported, of which 94.7% were hepatitis B. The majority of the affected individuals were 25–44 years old. HBV incidence was reduced by 12.71% annually between 2011 and 2016. However, the number of HCV patients increased during 2014–2016, and HCV incidence rate increased insignificantly (β = 0.109, P = 0.39).

Conclusion: There is a significant downward trend of HBV in East Azerbaijan due to mass vaccination programmes. In the case of HCV, when considering the availability of effective treatment regimens in addition to education and prevention programmes, policy-makers should focus on HCV screening and diagnosis, especially in the 25–44 age group.
Introduction

Viral hepatitis is a public health problem worldwide (1). According to the World Health Organization (WHO), in 2015 about 325 million people worldwide were affected by acute viral hepatitis, from which 275 million cases were related to chronic hepatitis B (HBV) and 71 million cases were related to hepatitis C (HCV) (2,3). Considering the high burden of hepatitis, WHO has aimed for a 30% reduction in the incidence of HBV and HCV by 2020 and a 90% reduction by 2030 (3).

The Eastern Mediterranean Region (EMR) countries have more than 15 million affected people and had the highest prevalence of HCV infection (4). Moreover, in this Region 21 million people had HBV (4). However, the Islamic Republic of Iran has a relatively low endemicity (5).

The prevalence of HBV varied across the Iranian provinces; the highest prevalence was reported in Golestan province (6.1%, 95% CI: 3.5–8.7%) (6) and the lowest prevalence was reported in Kermanshah (0.7%, 95% CI: 0.4–1.1%) (6). According to a recent systematic review, the pooled estimated prevalence of HBV infection was 2.2% in the general Iranian population from 1990 to 2016 (6). By initiating HBV vaccination programmes from 1993 and blood donor screening programmes from 1996, the improvement in incidence and prevalence rate of viral hepatitis has been expected. There are limited studies in the Islamic Republic of Iran that assess the HBV and HCV incidence trend. In a study in Ilam, Khazaei et al. reported...
the incidence of HBV and HCV during 2008–2013 and showed an increasing trend in HBV and HCV incidence (7). However, in a study in Hamadan during 2004–2009, a decreasing trend of HBV and HCV was reported (8). In East Azerbaijan, one of the most populous Iranian provinces, the prevalence of HBV and HCV was reported to be 1.2% in 2000 (9). However, no updated report about its prevalence or incidence is available.

Considering the importance of having updated information about the prevalence and incidence of hepatitis for the planning of prevention and treatments programmes, and the lack of studies in this regard in East Azerbaijan, this study was conducted with the aim of evaluating the trend of incidence rate of HBV and HCV during 2011–2016 in East Azerbaijan, Islamic Republic of Iran.

**Methods**

The data for this retrospective cohort study were obtained from the national notifiable disease surveillance system in East Azarbaijan province, which is the northwestern province in the Islamic Republic of Iran, and consists of 19 counties with a population of 3.909 million and borders the Republic of Azerbaijan and Armenia.

According to hepatitis management guidelines, monthly reporting of hepatitis cases (positive for HBsAg, HBeAg, anti-HBC and anti-HCV positive) from all laboratories, blood transfusion organizations, hospitals, health centres and district health centres are compulsory since 2004. Moreover, a questionnaire that includes demographic characteristics, risk factors, examination cause and disease status was completed by health staff based on the patient’s interview data. Finally, all data were registered in the province health centre database. For the present study, all subjects with positive HBsAg and anti-HCV serological markers who registered between 2011 and 2016 in East Azerbaijan province were included.

For estimating the incidence rate, the total population of East Azerbaijan, population of each county and also age-specific population for each year were obtained from the national Iranian census for 2016. The incidence rate for each year was calculated by the number of cases reported in a particular calendar year per 100 000 total population. The age-specific and also county-specific incidence rate was calculated as follows: (number of new cases) / (person-time at risk). Person-time at risk is calculated as follows: [(number of people at risk at the beginning of the time interval + number of people at risk at the end of the time interval) / 2] × (number of years in the time interval).

**Statistical analysis**
SPSS V25 and Microsoft excel 2013 were used for statistical analysis. The normality of distribution of continuous variables was tested by using the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviations (SD) and the categorical variables were presented as frequency (%). For determining the average annual rate of reduction or increase (AARR), the regression model was used for estimating beta coefficient and P-value. The log incidence rate and time were considered as dependent and independent variables respectively. Then AARR was calculated based on the following formula: AARR = (1-antilog beta)*100. The sign of beta indicates the direction of the trend. This method was adapted on the basis of information provided in a UNICEF technical note (10).

Results

Over the 6-year period (2011–2016), 3119 hepatitis cases in East Azerbaijan province were reported to the national notifiable diseases surveillance system; of these, 94.7% were HBV, 4.9% were HCV, and 0.4% were HBV and HCV co-infection. The mean age of the participants was 39.52 ± 14.76 years. The baseline characteristics of participants are shown in Table 1. The frequency of HBV was higher in females. However, the frequency of HCV and HBV–HCV co-infection was higher in males. As indicated, 89.31% of the cases were married and 55.47% were living in suburban areas. The frequency of HBV was higher in suburban areas; however, the frequency of HCV was higher in urban areas, and 87.81% of cases were chronic.

Figure 1 depicts the incidence rate of HBV and HCV stratified by year. According to this figure, there was a steady decrease in frequency and incidence rate of HBV between 2011 and 2016. The results of the regression analysis showed that the incidence rate of HBV decreased significantly (R2 = 0.89; β = -0.136, P = 0.005). HBV incidence rate was reduced by 12.71% annually from 2011 to 2016 (AARR = 12.71%). However, the number of HCV patients increased from 2014 to 2016. According to the regression analysis results, the incidence rate of HCV increased insignificantly (R2 = 0.18; β = 0.109, P = 0.39).

Figure 2 presents the frequency and incidence rate of hepatitis by age. The majority of individuals with HBV and HCV infections were 25-44 years old and the lowest frequency was seen in those under 5 years of age.

The frequency of HBV and HCV by counties is shown in Figure 3. The highest incidence rate of HBV was observed in Bonab county (28.33/100 000) followed by Hashtrood (26.54/100 000) and Malekan (22.99/100 000). The lowest incidence rate of HBV was observed in Varzagan county (2.03/100 000). In the case of HCV, the highest incidence rate was reported in Mianeh county (1.98/100 000). In Charoimag, Heris, Khodafarin and Varzagan no case of HCV was reported.
Discussion

In the present study, we aimed to determine the 6-year incidence rate of HBV and HCV in East Azerbaijan province. In total, from 2011 to 2016 there were 3119 hepatitis cases in East Azerbaijan reported to the national notifiable diseases surveillance system. The rate of HBV incidence in East Azerbaijan was similar to the incidence rate of HBV in Hamedan province (2004–2009) (8); however, it is lower than the reported incidence rate in Ilam province (200–2013). Moreover, we showed the downward trend in HBV incidence from 2011 to 2016 [17.74/100 000 (2011) to 10.22/100 000 (2016)], which may be due to the implementation of the vaccination programme in the country from 1993 (11). Previously, a decrease in HBV incidence after initiation of a vaccination programme had been reported in Italy (12). In addition to the vaccination programme, all blood donors were screened for hepatitis infection in the Islamic Republic of Iran from 1996 (13) and high-risk donors were eliminated; therefore, the transmission route was excluded. Furthermore, screening of pregnant women for hepatitis infection decreases the vertical transmission of hepatitis virus (14).

Considering the AARR = -12.71%, we are expecting that the incidence rate of HBV will reach 5.00/100 000 in 2020, which is in accordance with the WHO target for 2020 (30% reduction in HBV incidence compared with the 2015 baseline). The decreasing trend of HBV incidence has also been reported in previous studies; in Hamadan province the decrease in HBV incidence was reported from 2004 to 2009 (19.6 to 7.70) (8). Moreover, in studies conducted among blood donors in the Islamic Republic of Iran, the decline in the frequency of HBV infection has been reported (15–17). However, contrary to these results, Khazaei et al. (2018) showed an increase in HBV incidence from 2008 to 2013 in Ilam province (7). A similar increase was reported in Poland from 2005 to 2013 (18). The differences between the results of various studies may be due to the differences in region and also the time of the studies.

According to the results, the incidence rate of HCV had a decreasing trend from 2011 to 2013. However, the number of HCV patients increased from 2014 to 2016. A similar increase in HCV incidence has been reported in other studies in the Islamic Republic of Iran. In a study in Ilam province, the increasing trend in HCV incidence was reported from 2008 to 2013 (7). Moreover, Merat et al. reported an increase in HCV seroprevalence in the country (19). All Iranian HCV patients were treated using SOVODAK – a single pill containing Sofosbuvir and Daclatasvir – which has been shown to provide a 98% sustained virologic response (SVR) in HCV patients (20). Therefore, it is expected in this case that the WHO target for 2020 will be reached.

Unlike previous studies conducted in the Islamic Republic of Iran (7,8), the results of this study showed the higher incidence rate of HBV in females. Moreover, Merat et al. in a study in three Iranian provinces showed that there are no sex differences in the HBV prevalence rate. The
differences between the results of different studies may be due to the compulsory screening of hepatitis in pregnant women. On the other hand, in line with the results of the previous study (19), the incidence rate of HCV was higher in males than females. This can be attributed to the higher frequency of injecting drug use among males.

In accordance with the findings of earlier studies conducted in the Islamic Republic of Iran (7,8), the peak age for both HBV and HCV incidence was 25-44 years old. As a result of the initiation of the HBV vaccination programme in 1993, most of the under 25-year-old population was immunized for hepatitis B in 2016. Thus, as expected the incidence rate in these groups is very low. However, most of the people in the 25-44 years old age group were not immunized. On the other hand, people in this age group are of reproductive age and the frequency of marriage and consequently sexual contact between couples is high, which may affect hepatitis transmission. Moreover, the pregnancy rate in this age group is high. Therefore, the higher incidence rate in this age group could partly be attributed to implementing compulsory screening programmes of HBV in pregnant women.

More than 70% of participants in the present study did not define the exact risk factor for hepatitis transmission. In a study conducted by Centers for Diseases control and Prevention (CDC), more than 45% of cases did not report any known exposure risk (21). Considering that the main means of hepatitis transmissions are illegal (such as drug injection), most of the patients are unwilling to indicate the main route of transmission. In the present study about 20% of subjects had a positive HBV or HCV case in their household. The higher prevalence of hepatitis in family members, especially immediate relatives, had been reported in previous studies (7,22,23) that may be due to the horizontal mode of transmission and also the exposure to the same risk factors in the household (7).

According to the results, the prevalence of HBV was higher in certain counties including Bonab, Hashtrood and Malekan, which may be due to using unsterilized equipment for activities such as dental procedures, acupuncture, shaving, and hair cutting.

**Limitations**

In the present study we used the data of the national notifiable diseases surveillance system in East Azerbaijan. The limitations of this system, including underreporting due to the passive model of surveillance model, also apply to the present study. Moreover, the data for HCV were reported based on HCV anti-bodies in the present study that may prove to be false positive results. In addition, due to the asymptomatic nature of hepatitis, most patients were diagnosed accidentally. Therefore, the actual incidence of hepatitis may be higher. However, in the present study, we aimed to elucidate the trend of incidence over 6 years and it appears that this system
could provide a valuable means to achieve this aim.

**Conclusion**

The results of the present study showed the downward trend of HBV in East Azerbaijan, which is in accordance with the WHO target for 2020. Moreover, the low incidence of HBsAg among people aged under 25 years demonstrates the effectiveness of national vaccination programmes for neonates in reducing HBV infection. However, the incidence of HCV has insignificantly increased in recent years. Thus, considering the availability of effective treatment regimens for hepatitis C, policy-makers should focus on HCV screening and diagnosis in addition to implementing education and prevention programmes.

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**References**

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