

Systematic Review

Epidemiology of Hepatitis B in Iran from 2000 to 2016: A Systematic Review and Meta-Regression Analysis

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Abstract

Background: Hepatitis B infection is the major risk factor for liver cancer in Iran. There is no comprehensive population-based study on the prevalence of hepatitis B by regional distribution. Moreover, systematic reviews of hepatitis B prevalence lack knowledge of some regions. We aimed to estimate the prevalence of hepatitis B and its temporal trends over 17 years by sex, age and geographical distribution.

Methods: We used the Iranian Blood Donors data in addition to systematic reviews on population-based studies at national and provincial levels and statistical methods (A two-stage spatio-temporal model and crosswalk approach) to address the missing points of hepatitis B prevalence among the general population. The direct age-standardized approach was applied using Iran's national population in 2016.

Results: At national level, age-standardized hepatitis B prevalence in Iran decreased from 3.02% (95% uncertainty interval; 2.26 to 3.96) in 2000 to 1.09% (95% uncertainty interval; 0.85 to 1.37) in 2016, with a total -64.84% change. Hepatitis B prevalence was more than 1.3 times greater in males than females in 2016. Overall, the prevalence of hepatitis B increased with increasing age. At provincial level, in 2016, the province with the highest prevalence had a nearly 11-time greater rate compared to the lowest prevalence. The declining annual percent change (APC) of the prevalence trend varied between -11.53% to -0.5% at provincial level from 2000 to 2016. Only one province did not witness a downward trend in which the APC was 0.5% (95% UI:0.47-0.54).

Conclusion: The downward trend in prevalence of hepatitis B infection indicates the effectiveness of strategies and preventive measures adapted in Iran. Nevertheless, we need to eradicate this infection. In this regard, re-evaluating preventive measures, especially in high-risk age groups of the population, is recommended.

Keywords: Hepatitis B, Iran, Prevalence

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Introduction

Hepatitis B virus (HBV) is a public health concern, particularly in developing countries.¹⁻³ It is estimated that 257 million people live with HBV infection. Hepatitis B is one of the major risk factors for cirrhosis and hepatocellular carcinoma that caused 887 000 deaths in 2015.⁴ Since many individuals with chronic hepatitis B are not detected and treated properly, they are at risk of developing cirrhosis, liver failure, and hepatocellular carcinoma.²

In the WHO Eastern Mediterranean Region, the estimated prevalence of hepatitis B is nearly 3.3%.⁴ The

prevalence of hepatitis B varies in Iran's neighboring countries; it is 4.5%, 4.3%, 1.9%, and 1.6% in Turkey,⁵ Pakistan,⁶ Afghanistan,⁷ and Iraq,⁴ respectively. In Iran, according to a recent meta-analysis on survey studies, the prevalence of hepatitis B was almost 2%.^{8,9} The prevalence of hepatitis B in blood donors in Iran is reported at about 0.58%.¹⁰

Although viral hepatitis was a major global concern leading to higher mortality rates than serious infectious diseases such as HIV or malaria or tuberculosis in 2015, the issue has yet not been considered by policy makers.^{11,12} This situation is even worse in developing countries.⁶ It

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is important to screen at-risk provinces for chronic HBV infection to appropriately put the detected individuals under hepatitis care.

Overall, at provincial level, there are no appropriate detailed reports available to evaluate the population-based prevalence of hepatitis B in Iran. There are missing data on the prevalence of hepatitis B in some age groups, genders, and provinces in published systematic reviews. On the other hand, data on the prevalence of hepatitis B in blood donors are available for all provinces in the Iranian Blood Transfusion Organization. To address the missing data and to estimate this lack of information regarding different genders and age groups at population level, we aimed to evaluate the prevalence of hepatitis B at national and provincial levels from 2000 to 2016 by sex and age based on existing population-based reports and available blood donors' records.

Materials and Methods

Data Sources

Systematic Review Data Points

Data were gathered from published national or provincial population-based epidemiological studies on hepatitis B prevalence by sex between January 1, 2000 and January 1, 2016.

Blood Donor Data Points

Independent data of all positive HBV blood donors and the total number of individuals attending blood transfusion centers at national and provincial levels by sex, age, and type of donation were included. The ELISA kit for HBsAg was used to detect HBV.

Covariates

Aggregated covariates were obtained from the Statistical Center of Iran (SCI), demographic and health survey (DHS), including demographic characteristics such as age group, gender, years of schooling, urbanization, and wealth index.¹³

Systematic Search

Medline (PubMed), ISI Web of Science, Scopus, DARE, Iranian Digital databases (SID) (<http://www.sid.ir>), Barakat Knowledge network system (<http://health.barakatkns.com>), Irandoc (<https://irandoc.ac.ir/>) and Magiran (<https://www.magiran.com/>) were searched without time limitation and were restricted to "Iran". The mesh terms "Hepatitis B", "HBV," and "Iran", "prevalence" and their Persian parallels were searched in the titles and/or abstracts (Supplementary file 1). Duplicates were excluded. Then, titles and abstracts as well as full texts were evaluated by two independent researchers. Disagreements were resolved in group discussions with a third researcher. Finally, the prevalence of hepatitis B was extracted from population-based studies. Inclusion criteria included cross-

sectional or population-based cohort studies. Exclusion criteria included case reports, letters to the editor or correspondences, systematic reviews or meta-analyses, overlapping studies, prevalence of high-risk population groups and blood donors, low quality studies, or hospital-based studies and studies before 2000. The data extraction sheet included the author's name, year of study, province or city of the study, participant characteristics such as sex, age, sample size and HBV prevalence. All the studies had measured HBV by the ELISA method.

The quality of the included articles was assessed using the modified STROBE checklist (Supplementary 2). We also compared our results to two recently published systematic reviews and meta-analyses.^{8,9}

Statistical Methods to Deal with Data Gap

Spatio-temporal Bayesian Hierarchical Model

There are missing data on the prevalence of hepatitis B in some age groups, genders, and provinces. To address the missing data of blood donors and to estimate the prevalence and uncertainty intervals by sex, age, year, and province, two separate statistical models (the mixed model and spatio-temporal analysis) were developed.¹⁴ A matrix of 10 age-groups, 2 sexes, 31 provinces, and 17 years were included in the models.¹⁵ Using two different models reduces model dependency on the outcomes.

The conditional autoregressive model for the spatial random effects model was used. Measures that were geographically closer were expected to be more relevant than measures that had some distance. This model 'borrows information' from nearby time and provinces to improve estimations for missing values and/or a small number of observations. In addition, we checked the model validity by cross-validation methods and graphical plots.

Crosswalk Approach

Another problem is generalizing the prevalence of hepatitis B in blood donors to the general population. We used regression models to 'crosswalk' between blood donors and the general population's prevalence of hepatitis B.¹⁵ Using this approach, we predicted the correlation between hepatitis B prevalence of blood donors and population-based data by province, year, sex, and age groups.

Age standardization was done using Iran's population in 2016 to facilitate comparison between provinces. All methodological approaches are demonstrated in Figure 1 and Supplementary 3. We also compared the vaccinated group (who were born after 1993 and had hepatitis B on routine vaccination at birth) with other groups on the prevalence of hepatitis B. All programs were written in R statistical package (version 3.0.1) and Stata 14.

Results

This study includes 51 data points from systematic reviews. The characteristics of articles included in the

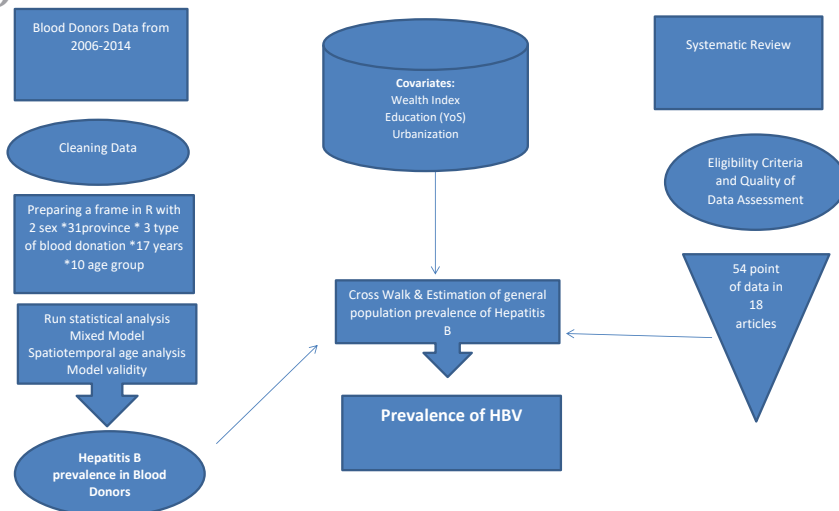


Figure 1. Summary of Method and Databases.

systematic reviews are presented in Supplementary 4; the PRISMA Algorithm is presented in Supplementary 5. Five hundred sixty-eight data points were included from blood donors. Other missing points were predicted by statistical modeling discussed earlier; R^2 adjusted for the crosswalk model was 75%.

At national level, age-standardized hepatitis B prevalence in Iran decreased from 3.02% (95% uncertainty interval; 2.26 to 3.96) in 2000 to 1.09% (95% uncertainty interval; 0.85 to 1.37) in 2016 with a total -64.84% change. In 2016, the age standardized hepatitis B prevalence in males was 1.25 (95% uncertainty interval; 0.98 to 1.57) and was more than 1.5 times greater than females at 0.93 (95% uncertainty interval; 0.98 to 1.57). The APC of hepatitis B prevalence was -5.26 in females and -6.82 in males (Figure 2, Table 1). Overall, with increasing age, the mean prevalence of hepatitis B increased at national level from 0.54% (95% uncertainty interval; 0.42 to 0.70) in the 15-20-year-old age group to 4.13% (95% uncertainty interval; 3.2 to 5.27) in the 60-65 year old age group (Figure 3, Table 2).

At provincial level, the highest and lowest age-standardized hepatitis B prevalence rates in 2016 were 4.03 (95% uncertainty interval: 3.07 to 5.20) and 0.34

(95% uncertainty interval: 0.26 to 0.44), respectively. The province with the highest prevalence had a prevalence rate nearly 11 times greater than that of the lowest rate. The hepatitis B prevalence trend has noticeably decreased during the 17 years of the study (Figure 4). At provincial level, in 2016, the province with the highest prevalence had a nearly 11 times greater rate compared to the lowest prevalence. The declining annual percent change (APC) of the prevalence trend varied from -11.53% to -0.5% at provincial level from 2000 to 2016. Only one province did not witness a downward trend in which the APC was 0.5% (95% UI: 0.47-0.54) (Table 1, Figure 2). The age-adjusted prevalence of hepatitis B at provincial level was higher in males than females in 2016. The sex ratio varied between 0.8 and 2.6 at provincial level. Although the sex ratio pattern was the same in 2000, ratios were higher than that in 2016 and varied between 1.17 and 3 (Figure 5). Overall, with increasing age, the mean prevalence of hepatitis B increased in all the provinces.

The prevalence of hepatitis B in the vaccinated group (who were born after 1993 and had routine hepatitis B vaccination at birth) was 0.70 (95% uncertainty interval: 0.63 to 0.77); in the unvaccinated group, it was 2.66 (95% uncertainty interval: 2.40 to 2.93).

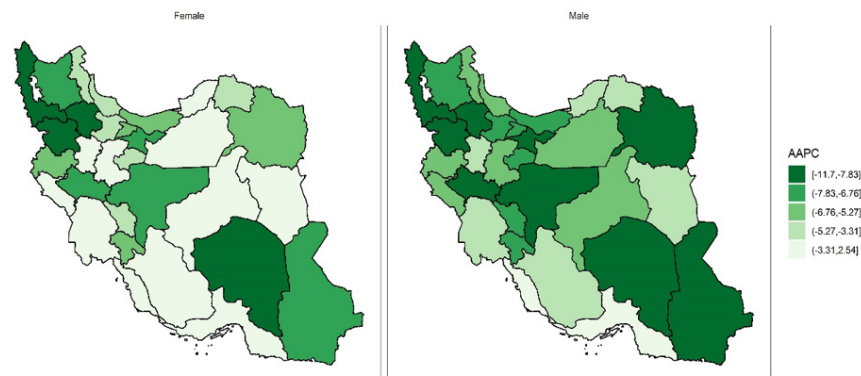


Figure 2. Annual Percent Change Map of Prevalence of Hepatitis B by Sex.

Table 1. Prevalence of Hepatitis B at National and Provincial Level in 2000 and 2016 and Average Annual Percent Change

National/Provincial	2000		2016		AAPC	
	Female (UI)	Male (UI)	Female (UI)	Male (UI)	Female (UI)	Male (UI)
Markazi	2.2 (1.64, 2.87)	4.62 (3.45, 6.09)	1.42 (1.11, 1.78)	1.83 (1.43, 2.29)	-2.65 (-2.71, -2.59)	-5.63 (-5.65, -5.6)
Gilan	1.1 (0.81, 1.47)	1.67 (1.24, 2.23)	0.54 (0.41, 0.7)	0.56 (0.44, 0.72)	-4.34 (-4.39, -4.3)	-6.54 (-6.57, -6.51)
Mazandaran	1.37 (1.05, 1.76)	2.4 (1.83, 3.1)	0.54 (0.43, 0.67)	0.7 (0.57, 0.87)	-5.71 (-5.76, -5.66)	-7.4 (-7.43, -7.37)
Azarbaijan East	2.23 (1.69, 2.89)	4.39 (3.3, 5.7)	0.68 (0.53, 0.85)	1.27 (1, 1.58)	-7.16 (-7.21, -7.12)	-7.47 (-7.49, -7.44)
Azarbaijan West	1.53 (1.16, 1.98)	3.63 (2.73, 4.71)	0.31 (0.25, 0.39)	0.7 (0.56, 0.87)	-9.34 (-9.43, -9.26)	-9.64 (-9.73, -9.55)
Kermnshah	2.19 (1.63, 2.87)	5.16 (3.82, 6.78)	0.76 (0.59, 0.96)	1.78 (1.39, 2.25)	-6.32 (-6.37, -6.27)	-6.45 (-6.48, -6.41)
Khuzestan	0.68 (0.51, 0.88)	1.29 (0.97, 1.68)	0.39 (0.31, 0.49)	0.58 (0.46, 0.72)	-3.26 (-3.32, -3.21)	-4.82 (-4.88, -4.76)
Fars	1.06 (0.8, 1.37)	1.92 (1.45, 2.49)	0.69 (0.55, 0.86)	0.82 (0.66, 1.02)	-2.57 (-2.66, -2.49)	-5.12 (-5.16, -5.09)
Kerman	3.22 (2.46, 4.17)	4.44 (3.35, 5.76)	0.88 (0.7, 1.09)	0.81 (0.65, 0.99)	-7.84 (-7.9, -7.78)	-10.14 (-10.17, -10.12)
Khorasan Razavi	1.52 (1.16, 1.96)	2.64 (1.98, 3.4)	0.56 (0.45, 0.69)	0.7 (0.56, 0.86)	-6.05 (-6.08, -6.03)	-7.95 (-7.95, -7.94)
Isfahan	1.47 (1.1, 1.92)	2.23 (1.66, 2.93)	0.44 (0.35, 0.56)	0.49 (0.39, 0.61)	-7.28 (-7.31, -7.25)	-9.03 (-9.05, -9.01)
Sistan and Baluchestan	4.02 (3.08, 5.09)	9.49 (7.23, 12.18)	1.17 (0.93, 1.44)	2.32 (1.85, 2.86)	-7.36 (-7.42, -7.31)	-8.4 (-8.43, -8.36)
Kurdistan	1.97 (1.48, 2.57)	5.4 (4.01, 7.09)	0.43 (0.34, 0.54)	1.01 (0.79, 1.27)	-9.01 (-9.06, -8.96)	-9.94 (-9.95, -9.92)
Hamedan	1.86 (1.39, 2.45)	3.52 (2.61, 4.64)	1.12 (0.87, 1.42)	1.8 (1.41, 2.29)	-3.07 (-3.13, -3.02)	-4.11 (-4.16, -4.06)
Chaharmahal and Bakhtiari	3.27 (2.42, 4.31)	6.88 (5.06, 9.15)	1.54 (1.18, 1.98)	1.92 (1.49, 2.46)	-4.72 (-4.81, -4.64)	-7.71 (-7.75, -7.66)
Loreshtn	2.48 (1.87, 3.22)	4.55 (3.42, 5.96)	0.73 (0.58, 0.92)	0.95 (0.75, 1.18)	-7.27 (-7.31, -7.24)	-9.31 (-9.34, -9.28)
Ilam	4.4 (3.21, 5.94)	9.7 (7, 13.09)	2.74 (2.04, 3.59)	3.94 (2.97, 5.17)	-2.98 (-3.03, -2.93)	-5.53 (-5.58, -5.48)
Kohgiluyeh and Boyer Ahmad	2.01 (1.47, 2.68)	6.22 (4.54, 8.36)	0.7 (0.53, 0.91)	1.89 (1.45, 2.45)	-6.39 (-6.45, -6.34)	-7.19 (-7.24, -7.15)
Bushehr	1.87 (1.36, 2.53)	4 (2.9, 5.44)	1.98 (1.5, 2.6)	3.07 (2.34, 3.98)	0.33 (0.27, 0.39)	-1.65 (-1.67, -1.63)
Zanjan	1.69 (1.24, 2.24)	3.28 (2.41, 4.38)	0.25 (0.19, 0.33)	0.44 (0.34, 0.57)	-11.18 (-11.25, -11.11)	-11.74 (-11.83, -11.66)
Semnan	3.74 (2.8, 4.89)	6.42 (4.78, 8.47)	3.04 (2.35, 3.84)	2.43 (1.88, 3.08)	-1.24 (-1.37, -1.12)	-5.84 (-5.9, -5.78)
Yazd	2.13 (1.57, 2.83)	4 (2.95, 5.34)	1.37 (1.04, 1.76)	1.67 (1.29, 2.13)	-2.89 (-3.11, -2.67)	-5.31 (-5.37, -5.26)
Hormozgan	1.92 (1.44, 2.49)	3.81 (2.85, 4.98)	2.84 (2.22, 3.59)	3.32 (2.62, 4.17)	2.54 (2.5, 2.58)	-0.79 (-0.84, -0.73)
Tehran	2.71 (2.07, 3.45)	3.18 (2.42, 4.08)	0.84 (0.68, 1.01)	0.73 (0.59, 0.89)	-7.17 (-7.22, -7.12)	-8.81 (-8.85, -8.77)
Ardabil	2.85 (2.15, 3.67)	7.36 (5.51, 9.56)	1.4 (1.1, 1.76)	2.77 (2.18, 3.48)	-4.21 (-4.32, -4.1)	-5.84 (-5.9, -5.78)
Qom	2.46 (1.82, 3.27)	5.47 (4.01, 7.29)	1.14 (0.88, 1.46)	1.48 (1.14, 1.89)	-4.74 (-4.82, -4.66)	-7.82 (-7.92, -7.72)
Qazvin	2.13 (1.54, 2.87)	3.72 (2.69, 5.05)	0.93 (0.7, 1.22)	1.06 (0.8, 1.38)	-5.07 (-5.11, -5.04)	-7.53 (-7.57, -7.48)
Golestan	4.44 (3.41, 5.65)	9.62 (7.33, 12.33)	2.7 (2.15, 3.31)	4.5 (3.61, 5.54)	-3.11 (-3.15, -3.08)	-4.64 (-4.66, -4.63)
Khorasan North	4.65 (3.51, 6.04)	7.89 (5.9, 10.35)	2.19 (1.7, 2.77)	3.39 (2.65, 4.27)	-4.55 (-4.61, -4.49)	-5.1 (-5.15, -5.05)
Khorasan South	4.71 (3.47, 6.26)	8.92 (6.53, 11.92)	2.87 (2.18, 3.71)	5.2 (3.97, 6.7)	-2.99 (-3.06, -2.91)	-3.35 (-3.38, -3.32)
Alborz	5.1 (3.42, 7.43)	6.31 (4.21, 9.26)	1.89 (1.33, 2.62)	1.76 (1.25, 2.46)	-6.12 (-6.18, -6.06)	-7.62 (-7.66, -7.58)
Iran	2.2 (1.65, 2.88)	3.85 (2.87, 5.05)	0.94 (0.73, 1.18)	1.25 (0.98, 1.58)	-5.26 (-5.33, -5.19)	-6.82 (-6.86, -6.77)

AAPC, average annual percent change; UI, uncertainty interval.

Discussion

Based on our results, age-standardized hepatitis B prevalence decreased over the 17 years of the study at national and provincial levels. Age-standardized hepatitis B prevalence in males was more than 1.5 times greater than in females. Moreover, the APC of hepatitis B prevalence in females was higher than in males. Overall, with increasing age, the prevalence of hepatitis B increased in all the provinces.

The prediction prevalence in this study is very similar to previous population-based surveys in Iran. The predicted prevalence of hepatitis B in males in 2012 in Chaharmahal and Bakhtiari was 2.9% versus 2.7% in the observed

survey report,¹⁶ or 1.7% in Isfahan in 2005 versus 1.3% in the observed survey report.¹⁷

The World Health Organization's strategy for eliminating viral hepatitis B by 2030 includes global objectives to decrease new viral hepatitis infections by up to 90%. Additionally, the 65% reduction in mortality due to viral hepatitis is another objective, particularly the reduction of HBV and hepatitis C virus related mortalities. Therefore, the declining trend of hepatitis B observed in this study is in line with this strategy.

Iran has a twice lower hepatitis B prevalence than its neighboring countries like Turkey and Pakistan.^{5,6,16} However, it has not been eliminated yet and remains the

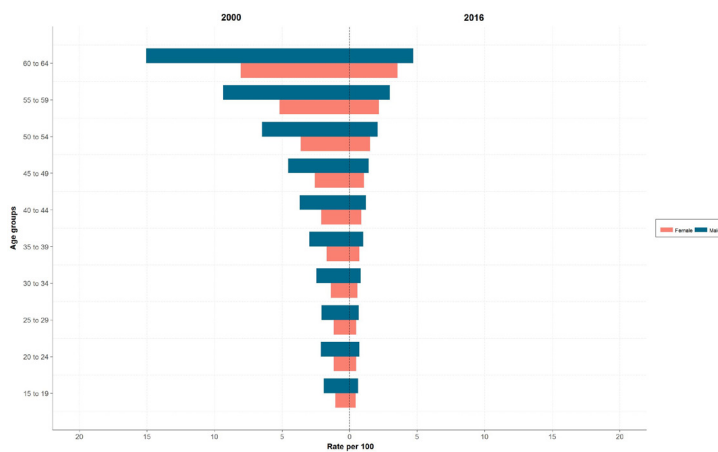


Figure 3. Prevalence of Hepatitis B by Age Categories in 2000 And 2016.

main cause of death due to liver cancer and cirrhosis.^{3,17} Therefore, special emphasis should be laid on this objective. Disease prevention is key. This may include reducing the risks of exposure to the viruses, vaccination, and early detection and treatment. As acute hepatitis infections are frequently asymptomatic, detection is a major problem in many countries.¹¹ Based on the literature, in most Asian and African countries and Iran, hepatitis B infection was found more frequently than hepatitis C infection in liver cancer patients.³ This situation is reversed in Europe, the United States, Japan, Pakistan, Mongolia, and Saudi Arabia.¹⁸ It is estimated that in Iran, by 2035, the number of newly detected hepatitis B cases will be 2.5 times lower than that in 2016, but the cirrhosis percentage due to hepatitis B will be almost doubled.¹⁶ Vaccination is the key solution in many countries, particularly in Africa and Asia. In Iran, this strategy was established in 1993, and the HBV infection has declined in children and young adults, consistent with the results of this study.^{19,20} This could be the reason behind the reduction in prevalence among the 25-30-year-old age group in this study.

The Polaris Observatory estimated that 48 million

children lived with HBV in 2016. According to recent documents and this study, due to vaccination, newly detected HBV positivity is on the decline, but hepatitis B infection is still observed in individuals under the age of 25 years according to the present study's results.

Children and childbearing women are still a challenge due to mother-to-child transmission of chronic viral hepatitis.²¹ Furthermore, it has been reported that HBV-positive childbearing women had higher viral loads compared to others.²² Thus, developing comprehensive preventive programs for childbearing women by policymakers is recommended.¹⁶ Studies have shown that preventive strategies for mother-to-child transmission through screening and treatment have led to HBV elimination in sub-Saharan Africa.²³⁻²⁵ This could be added to Iran's preventive protocol for HBV elimination.⁵

An earlier study showed that females were more likely to produce antibody against hepatitis B than males in reaction to infection, and males became carriers of chronic hepatitis B more frequently.²⁶⁻²⁸ This is consistent with our results of the trend in females and the percentage change of hepatitis B prevalence over the 17-year period. The next

Table 2. Prevalence of Hepatitis B at National Level by Age and Sex, in 2000 and 2016

Age Group	2000 (UI)		2016 (UI)	
	Female	Male	Female	Male
15-19	1.05 (0.78, 1.4)	1.92 (1.42, 2.55)	0.45 (0.35, 0.58)	0.64 (0.49, 0.82)
20-24	1.17 (0.87, 1.54)	2.11 (1.56, 2.78)	0.5 (0.39, 0.63)	0.71 (0.56, 0.9)
25-29	1.17 (0.87, 1.53)	2.07 (1.54, 2.73)	0.5 (0.39, 0.63)	0.69 (0.54, 0.87)
30-34	1.38 (1.03, 1.82)	2.44 (1.82, 3.22)	0.59 (0.46, 0.74)	0.81 (0.64, 1.02)
35-39	1.69 (1.26, 2.22)	2.99 (2.22, 3.92)	0.72 (0.56, 0.91)	1.01 (0.79, 1.26)
40-44	2.09 (1.57, 2.72)	3.68 (2.75, 4.83)	0.87 (0.68, 1.09)	1.21 (0.95, 1.52)
45-49	2.56 (1.93, 3.34)	4.53 (3.39, 5.96)	1.07 (0.84, 1.34)	1.42 (1.12, 1.78)
50-54	3.62 (2.73, 4.72)	6.48 (4.85, 8.47)	1.52 (1.2, 1.91)	2.08 (1.64, 2.6)
55-59	5.18 (3.92, 6.72)	9.36 (7.02, 12.2)	2.18 (1.72, 2.73)	2.99 (2.35, 3.75)
60-64	8.06 (6.06, 10.47)	15.04 (11.21, 19.73)	3.56 (2.75, 4.55)	4.72 (3.66, 6.01)

UI, uncertainty interval.

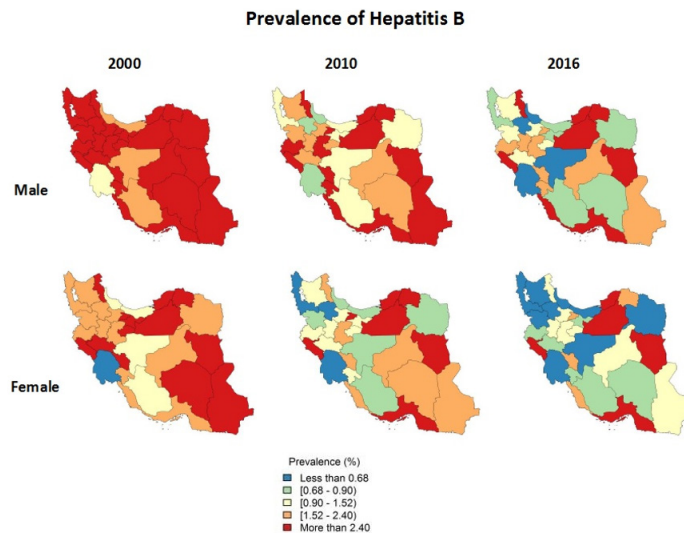


Figure 4. Prevalence of Hepatitis B Map by Province in 2000, 2010 and 2016.

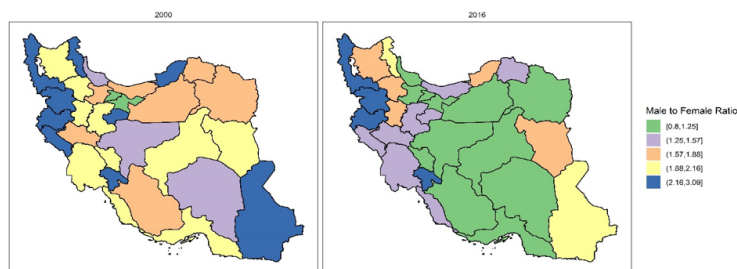


Figure 5. Female to Male Ratio of Hepatitis B Prevalence in 2000 and 2016.

step is to clarify what should be done next.

The role of medical providers in eliminating hepatitis B could be detection of HBV-positive patients, treating them and referring them to psychotherapy if needed, adapting preventive measures to minimize the risk of transmission to others, and referring patients to chronic liver disease specialists to minimize the risk of developing future cirrhosis or hepatocellular carcinoma. Assessment of HBV replication status and severity of liver injury must be also borne in mind.²⁹ Policymakers and medical providers should establish a lifelong assessment process for all hepatitis B-positive patients to monitor liver disease or cancer progression, and start early treatment and screen responses to treatment.²⁹ The choice of antiviral therapy for hepatitis B is not curative, but can slow down the progression of the disease and improve survival.²¹ However, hepatitis B therapy is a rapidly changing area of clinical practice.²⁹

In this respect, establishing a registration system for seropositive chronic viral hepatitis patients is recommended. Formation of a registry enables medical providers and policymakers to provide direct medical management, counseling, notifications, patient follow-up, and to have national, provincial and regional estimates of identified

chronic hepatitis B infection rates. Other benefits of these registries are identifying HBV's epidemiologic transitions, treatment success, cancer and liver disease development and monitoring the screening and prevention programs at national, provincial and regional levels. To this end, it is necessary to establish high-quality electronically designed laboratories across the country and methods to prevent duplication of registries. Moreover, for better data gathering and future estimates on the trends and burden of diseases, this registry must be connected to the perinatal screening of women and neonates affected with chronic hepatitis and also to the liver cancer registry and death certificate data.²⁹ The Iranian Hepatitis Network has been established by Iran's gastroenterologists to achieve the hepatitis elimination strategy.³⁰

Nowadays, medical acquiescence is high for testing seropositivity of hepatitis B in certain populations like pregnant women or those who are admitted to hospitals, but it is still necessary for policymakers to facilitate detection and testing of chronic HBV patients in the following: primary care systems, physician's offices, TB health centers, substance abuse centers, refugee offices and health centers, academic or organizational clinics, dialysis, and cancer centers.²⁹ According to the literature, we do have

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the instruments to eliminate viral hepatitis by vaccination (hepatitis B) and through curative treatment (hepatitis C)^{11,21}; however, all policymakers and governments should adopt preventive, diagnostic and treatment strategies at a global level.

The strength of this study was its reporting of hepatitis B prevalence over 17 years for all the provinces, both sexes and 10 age groups for the first time using the latest statistical modeling.

As a limitation, our blood donor data was subject to selection bias. Donors have different motivations and attitudes compared to the general population. We checked the trend in weight, as well as systolic and diastolic blood pressure (as independent covariates) of Iranian blood donor data with the national non-communicable diseases risk factors survey (STEPs)^{31,32} which is a population-based survey in the country, and found that the patterns were similar. Thus, another strength of this study was that we applied the latest statistical modeling to predict the general population's prevalence from blood donors using population-based covariates¹³ and published population-based surveys.

In conclusion, Iran has a low prevalence rate of hepatitis B compared to its neighboring countries and is witnessing a downward trend. Nevertheless, the following steps are recommended to achieve the 2030 Elimination Objective; improving diagnostic strategies, providing better treatment options especially for high-risk groups, discovering and developing functional cures for hepatitis B, knowledge development on the disease, reducing stigma and raising public awareness. Furthermore, establishment of hepatitis B registry networks is useful for clinical management and alleviation of public health concerns. Last but not least, since having knowledge of the disease and fighting stigmas are highly important in preventive strategies, patient education programs should be directed in a culturally sensitive style and easy understanding by any level of education and in the patient's native language.

Authors' Contribution

NR, MP and MM: Writing the original draft. MAL, SKh, SAM, MZ, SAK, FD, ShA and FF: Writing, review and editing. ASH, KG and MP: Methodology, Validation and Software. FF: Supervision.

Conflict of Interest Disclosures

There is no conflict of interest.

Ethical Statement

This study was approved by ethical committee of Iran University of Medical Sciences (IR.IUMS.REC1395.9221128201).

Supplementary Materials

Supplementary file 1. Search strategy in Medline.

Supplementary file 2. Quality assessment of articles by STROBE checklist.

Supplementary file 3. Statistical analysis detail.

Supplementary file 4. Characteristics of included articles in systematic search.

Supplementary file 5. PRISMA algorithm.

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Supplementary file 1. Search Strategy in Medline

Search 1. Epidemiology

"prevalence" OR "incidence" OR "epidemiolog\$" OR "data collection" Or "Survey" OR "surveillance"
OR "screening" OR "seroprevalence" OR "cohort" OR "population study" OR "population sample" OR
"population survey" OR "population surveillance" OR "community sample" OR "rapid assessment" OR
"cross sectional" OR "General population"

Search 2

HBV OR "Hepatitis B virus" OR "Hepatitis B " [title, original title, abstract, name of substance word,
subject heading word, Mesh term] OR HBV seropositivity OR HBV seroprevalence OR HBV
serodiagnosis

Search 3

Iran

Medline search strategies:

COMBINE : Search 1 AND Search 2 AND Search 3

Supplementary file 2. Quality Assessment of Articles by STROB Checklist.

TOTAL (n = 18)				
STROB Items	Adequacy(Number of Articles)			%
	NA	NO	YES	
1A	0	7	11	61.11
1B	0	0	18	100
2	0	0	18	100
3	0	0	18	100
4	0	0	18	100
5	0	0	18	100
6	0	3	15	83.33
7	0	3	15	83.33
8	0	0	18	100
9	0	3	15	83.33
10	0	4	14	77.77
11	0	3	15	83.33
12A	6	3	9	75
12B	6	3	9	75
12C	13	3	2	40
12D	13	3	2	40
13A	0	3	15	83.33
13B	13	0	5	27.77
14A	0	0	18	100
14B	0	6	12	66.66
15	0	3	15	83.33
16	0	0	18	100
17	14	0	4	100
18	0	0	18	100
19	0	17	1	5.55
20	0	0	18	100
21	0	0	18	100
22	0	0	18	100
Mean Total Quality	2.24	2.20	13.89	84.03

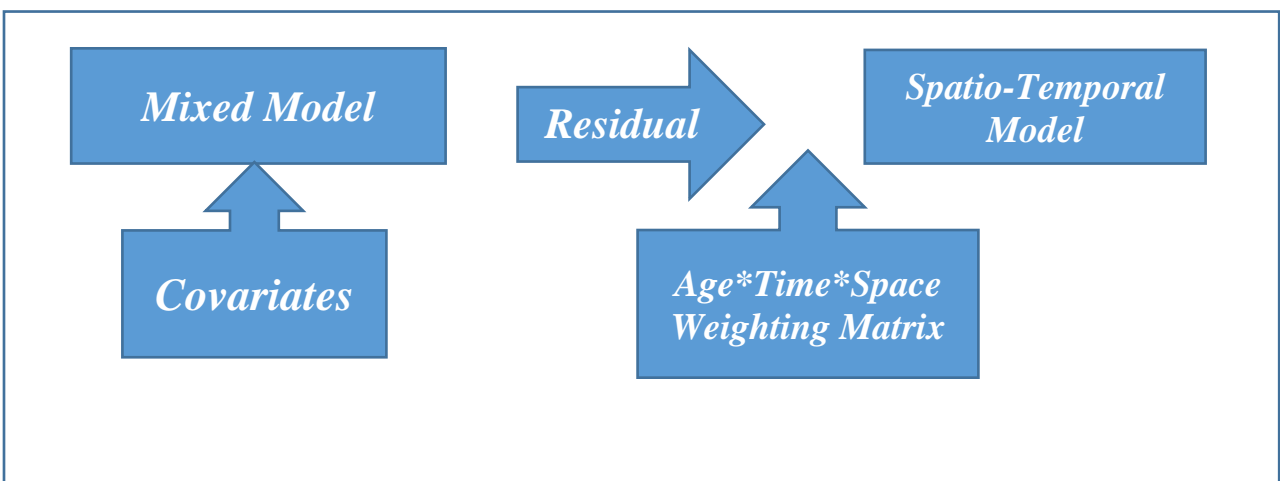
Supplementary file 3. Statistical Analysis Detail

Spatio-temporal models are used when the study data is collected geographically and also over time. Both spatial and temporal dimensions must be considered simultaneously when analyzing these data. In other words, considering only one temporal or spatial dimension of the correlation does not take into account the other dimension, thereby reducing the study power. The model used in this study should be capable of taking into account spatial and temporal correlations simultaneously. It is also important to consider the differences between age and sex in the estimates of this model. This model consists of two components. First, a random effects model was fitted to the data. The fitted model was defined as follows:

$$\text{Logit}(\text{prevalence rate}) = \alpha + \beta_1 \text{sex} + \beta_2 \text{age} + \beta_3 \text{year} + \beta_4 \text{YOS} + \beta_5 \text{WI} + \beta_6 \text{urbanizratio} + b_i$$

The variables used in this model include mean mean years of education (YOS) and household assets index (WI), and urbanization as a covariate and population logarithm as a compensation variable to improve prediction values. Also the random effect b_i is related to each province. Second, the predicted response values and residuals were extracted from this model. The residuals of this step were used in the spatio-temporal model to investigate the effects of variables such as age, sex, time, and location that the random effects model could not justify.

The procedure used for the spatio-temporal model is that any data in the dataset can affect other data. The magnitude of this effect varies depending on the spatio-temporal as well as the proximity of the two data sets. The effects are calculated and weighted for each of the temporal, spatial, and age correlations by their proximity matrices. Finally, by combining these three matrices, the overall weighting matrix is obtained. By applying this matrix to the data, we obtain the expected values of the residuals for the predicted values. Finally, the sum of the predicted residuals of this step and the predicted values of the regression model of the random effects of the final estimated values are obtained.



A simple exponential function was used to form the age variable weight matrix as follows:

$$W_{a_{i,j}} = \frac{1}{e^{\omega * (\text{agegroup}_i - \text{agegroup}_j)}}$$

As it is evident, with increasing distance between the two age groups, the assigned weight decreases. Also if two observations are in the same age group have the highest weight possible. The parameter ω plays a decisive role in model estimations. For cases with thin data, decreasing the ω parameter can increase the level of smoothing on the age variable. On the other hand, when the difference between age groups is high, the smoothing rate of the model on the age variable can be reduced by increasing the ω value.

To construct the time-weight matrix, a matrix scheme similar to that used in the local Loess regression was used. This scheme is defined as follows:

$$W_{t_{i,j}} = (1 - (\frac{|year_i - year_j|}{\text{argmax}(|year_i - year_j|) + 1})^\lambda)^3$$

As we can see here, by increasing the interval of the two observations, the weight of the observations decreases and vice versa. The main difference between the above scheme and that used in the Loess model is the existence of a parameter λ that can control the smoothness of the results on the time variable. This value is determined by the number and distribution of data, as stated for the age variable.

the matrix with zero and one elements was used to model spatial correlation in the model. A matrix with 31 columns and rows was formed. Each row and column of this matrix represented one of the provinces of the country. If the two provinces had a common boundary, for the same row and column as their common border, the number was one, and if they had no neighborhood, the value was zero.

Finally, all three weight matrices of age, time and place were multiplied to obtain the final weight matrix. Finally, after applying this weight matrix to the model residuals, the residuals adjusted to the predicted amount of the model were combined and the final results were obtained.

Different methods were used to obtain the uncertainty rates at different stages. The first stage variance was closed form. But in the second step, due to the complexity of the calculations and the fact that it was virtually impossible to calculate the variance of estimates by mathematical methods, the simulation was used. The method used was to estimate the values of the random effects model with their variance. Then the random values of the normal distribution were estimated with the mean values. This process was performed 1000 times. Thus, based on the percentiles of the values obtained, the point and distance estimates of the required values were obtained.

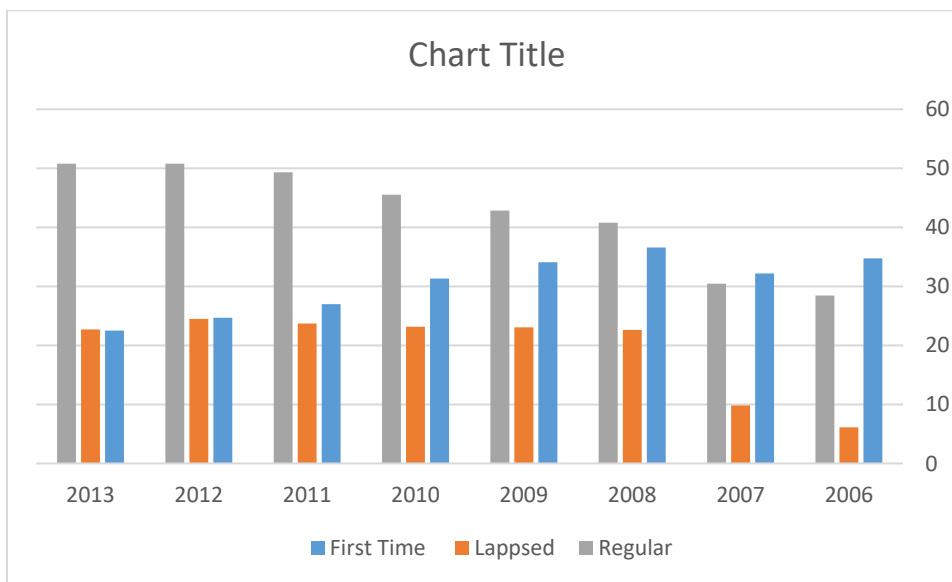
Cross Walk :

A crosswalk is a specification for mapping one metadata standard to another. Crosswalks provide the ability to make the contents of elements defined in one metadata standard available to communities using related metadata standards. We have used linear regression model using logit transformation and covariates (urbanization ,education, and welth index) to enhanced mapping . The RMSE has a "unite" value and the RMSE is not

directly comparable for different "unite" values. However, RMSE values can be predicted for detecting model performance in a calibration period using a validation period as well as comparing individual model performance with other models.

$$RMSE = \sqrt{\frac{\sum_{i=1}^n (X_{obs,i} - X_{model,i})^2}{n}}$$

To do cross-walks, both sets of data must contain at least some combination of information. Since the blood transfusion data had nothing to do with systematic reviews data, we had to first predict all possible combinations using the spatio-temporal analysis model in the blood transfusion data, and then use this information and cross-sharing points. The blood transfusion data contained three different types of donors: first-time, with previous history, and regular. A first-time donor is a donor who came to donate blood for the first time. So their risk of infection is high despite initial screening of donors by a physician, and fortunately they are less than half of blood donors. Regular blood donors are persons who donate blood at least 3 to 4 times a year. With history blood donors are people who donate blood at least once a year, and these individuals have a lower risk of infection than the first-time blood donors. In this study, a systematic search was done on the numbers and ratio of different types of donation in each year from the literature review and used as weight cores to aggregate the Blood Transfusion data to initiate cross-walk. This gave us a better estimate and our results were similar to population-based studies.



Finally, using the regression model, the correlation between the systematic review data of hepatitis B and the hepatitis B prevalence data in blood donors was calculated by age, sex, and province using the cross-walk method. The prevalence of hepatitis B was estimated in areas without data. The challenge with blood transfusion data is that we cannot consider the donor population to be the same as the normal population, and we used the

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cross walk method to generalize it to the normal population. Four regression models were performed with log, logit, squared root, norm prevalence, and the best fit model was the logit model used.

The covariate data were obtained from the Iranian Center for Statistics, Demography and Health Survey (DHS) which included demographic characteristics such as age group, gender, school year, urbanization, wealth index.

To determine the degree of uncertainty, the spatio- temporal model error values were used. RMSE was also used to estimate the model validity.

For age standardize , the national population data of Iran in 2016 was used.