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Estimating the Prevalence of Hepatitis B Virus Infection and Exposure Among General Population in Iran

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Abstract

Context: Accurate and updated data describing hepatitis B virus (HBV) epidemiology is crucial for development of national policies to control HBV infection in each country. This study was conducted to estimate the prevalence of HBV infection and exposure in Iran, using the available provincial data.

Methods: MEDLINE, Web of Science, Scopus, Google Scholar, and Scientific Information Database were searched for studies assessing the prevalence of hepatitis B surface antigen (HBs Ag) or hepatitis B core antibody (anti-HBc Ab) among the general population between 2006 and 2016 in at least one city of Iran. National prevalence was estimated by two methods. Method 1 used only prevalence estimates of provinces with available survey data. In method 2, all provinces were classified based on the risk of HBV infection among blood donors. HBV prevalence in provinces with missing data was extrapolated from the provinces with available data, and with comparable risk of HBV infection among blood donors. In both methods, national prevalence was estimated using pooled provincial prevalence estimates, weighted by the province population size.

Results: Thirteen studies from 12 provinces were included. The prevalence of HBs Ag and anti-HBc Ab varied markedly across provinces. Provincial HBs Ag prevalence ranged from 0.76% to 5.10% (I-square = 91.7%) and provincial anti-HBc Ab prevalence ranged from 4.17% to 36.90% (I-square = 99.3%). Using method 1, the national prevalence of HBs Ag and anti-HBc Ab was estimated as 1.84% (95%CI: 1.61%, 2.09%), and 13.59% (95%CI: 12.92%, 14.29%), respectively. Using method 2, the national prevalence of HBs Ag was estimated as 1.79% (95% uncertainty range: 1.67%, 1.91%), equating to 1,347,000 (1,253,000 - 1,434,000) individuals living with chronic HBV infection in Iran. The prevalence of HBs Ag and anti-HBc Ab was higher among men compared to women.

Conclusions: HBV prevalence in Iran is low, and has decreased over past decades. However, the risk of HBV infection varies across provinces with some provinces having high HBV prevalence. More detailed data of the HBV epidemiology and transmission in provinces where HBV infection is endemic could support designing the appropriate interventions to control HBV epidemics.

Keywords: Hepatitis B, Prevalence, Iran, HBs Ag, Anti-HBc Ab, Epidemiology, Systematic Review

1. Context

The World health organisation (WHO) has set a goal for elimination of hepatitis B virus (HBV) infection as a public health threat by 2030, defined as 90% reduction in HBV incidence and 65% reduction in HBV-related mortality (1). Accurate and updated data describing the HBV epidemiological profile is crucial for understanding the epidemics in each country and consequently for the development of national policies to achieve WHO HBV elimination targets.

There was no estimate of the national prevalence of HBV exposure, defined as positive HBV core antibody (anti-HBc Ab), in Iran although several studies reported the prevalence at a city or province level (2-10). The prevalence of HBV infection, defined as positive HBV surface antigen (HBs Ag) in Iran was estimated as 1.7% in 1991 and 1999 (11), and 2.1% during 2001 - 06 (12). Two recent studies, using meta-analysis, estimated HBV infection prevalence in Iran as 1.3% during 2010 - 13 (13), and 2010 - 16 (14). Given that these two studies used standard meta-analysis methods to pool the city/province-level prevalence values to estimate the national prevalence, the estimates may have been subject to potential bias towards studies with a large sample

size but from cities/provinces with small population size. Moreover, given that only a small number of provinces have available prevalence data, a methodology which also considers provinces with unavailable data is preferred to provide more accurate national-level prevalence estimate.

The current study used a more sophisticated methodology to estimate the prevalence of HBV infection and exposure in Iran, using the available provincial data over the last 11 years (2006 to 2016).

2. Methods

The reporting style of this study was based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (15). The PRISMA statement was originally developed for systematic reviews of studies evaluating healthcare interventions. We customized PRISMA components to fit the scope of the current study.

2.1. Eligibility Criteria

Population-based surveys investigating the prevalence of HBs Ag or anti-HBc Ab among the general population were included if they met all of the following criteria:

a) The study population was representative of "general population".

b) The participant recruitment process covered at least one major city of a province.

c) The study was conducted in 2006 or after.

d) The study was published in English or Persian

Studies restricting the study population to specific age cohorts, a gender or population subgroups (e.g. blood donors, health care workers, university students, prisoners, etc.) were excluded.

2.2. Information Sources

A literature search of four bibliographic database, including MEDLINE (OvidSP), Scopus, and web of science core collection for English records, and Scientific information database (www.sid.ir) for Persian records was performed on January 2017, covering all studies published from January 2006 to December 2016.

The web of Science core collection consists of five databases including Science citation index expanded (SCI-EXPANDED), social sciences citation index (SSCI), conference proceedings citation index- Science (CPCI-S), conference proceedings citation index- social Science and humanities (CPCI-SSH) and emerging sources citation index (ESCI). Grey literature was searched through Google Scholar. Reference lists of selected articles and relevant review articles found during the initial search were hand searched. Forward citation tracking were carried out, using Scopus, to identify further potentially relevant studies.

2.3. Search Strategy

A sensitive search strategy was used to ensure that all relevant studies were captured. The search strategies were described in detail in Supplementary file Appendix 1. In brief, the search strategies were based on ("Hepatitis B" OR HBV OR HBsAg OR HBcAb) AND (Iran OR (name of each province and province capital cities)). This combination of terms was used for searching article title, abstract or keywords. In MEDLINE, the relevant medical subject heading (MeSH) terms were also used. No language and study type was limited in search strategies. Scientific information database was searched for studies published in Persian, using the Persian equivalent term for "hepatitis". Google Scholar was searched using both English and Persian search terms.

2.4. Study Selection

The records found through database searching were merged and duplicates removed using EndNote X7 (Thomson Reuters, New York, NY, USA). Records were initially screened by title and abstract to exclude those not related to the current study and multiple reports from the same studies. The full-text of potentially eligible records were retrieved and examined.

2.5. Data Collection Process

The following items were extracted from each article: first author (as the study identifier), study year, study province/city, sampling method, study population size, study population gender ratio and age distribution, laboratory assays used to measure HBs Ag and anti-HBcAb, and the number and the prevalence of participants with positive HBs Ag and anti-HBc Ab (overall and by gender). Authors were contacted when the required data had not been reported in the paper.

2.6. Risk of Bias in Individual Studies

The quality of eligible studies were assessed using a critical appraisal tool, specifically developed for the prevalence studies (16). Various methodological features of the studies were assessed using this tool, including representativeness of the study population, participant recruitment process, sample size, study setting, response rate, outcome measurement, and statistical analysis. The tool has 10 items. Each study was given zero or one score for each item. Studies with a total score of > 7 were considered to have low risk of bias.

Every stage of study selection, data extraction, and critical appraisal was carried out by two reviewers independently, with discrepancies discussed with a third reviewer to reach consensus.

2.7. Synthesis of Results

For each study, the overall and gender-specific prevalence of HBs Ag and anti-HBc Ab, and corresponding standard errors and 95% confidence intervals (95%CI) were calculated. In studies conducted in one city, the reported prevalence was extrapolated to the province. The prevalence estimates of different studies from one province were pooled using meta-analysis methods. The study prevalence estimates were displayed using the forest plots. Heterogeneity was assessed using the I-square statistic, with an I-square < 50%, 51% - 75%, and > 75% being considered as low, medium, and high heterogeneity, respectively.

In the standard meta-analysis methods, the weight of each study is based on the standard error which is primarily affected by the study sample size. This means that a study with a larger sample size has a stronger impact on the pooled estimate. The current study aimed to pool the prevalence estimates in provincial levels to estimate the national prevalence. In this instance, the province population size is expected to have a stronger impact on the pooled estimate than the study sample size. Two methods were used to estimate the national prevalence based on the provincial prevalence estimates, while in both methods survey analysis principles were used to pool the provincial prevalence estimates, with each study (province) being considered as a cluster.

Method 1: National prevalence of HBs Ag and anti-HBc Ab was estimated using the prevalence estimates of the provinces with available studies. The results of each study were initially expanded based on the study sample size and then weighted based on the proportion of the province population size to the study sample size. Province population sizes were extracted from the national population and housing census in 2011 (1390), reported by the statistical center of Iran (https://www.amar.org.ir). A sensitivity analysis was conducted including only the studies with a low risk of bias (quality assessment score > 7) to assess if potential biased results in single studies could affect the national prevalence estimate.

Method 2: National HBs Ag prevalence was estimated using the prevalence estimates of all provinces while the prevalence in provinces with no available study were estimated based on the provinces with available study, who had a similar risk of HBV infection based on the prevalence in blood donors. In the first step, all provinces were classified into three strata (low-risk, medium-risk, and high-risk) based on the average of provincial prevalence of HBs Ag in blood donors during 2011 - 2015 (Table 1). In each stratum, the prevalence estimates of provinces with available low-bias study (quality assessment score > 7) were pooled, using the principles explained in the method 1, and the pooled estimate extrapolated to the provinces with no available study. In the second step, the provincial prevalence estimates were weighted based on the province population size while the national prevalence estimates were computed based on the average of the weighted provincial estimations.

Table 1. The Average Prevalence of HBs Ag Among Blood Donors During 2011 - 2015 in Each Province

Province	HBs Ag Prevalence, %	Risk Group
Gillan	0.038	Group 1
Fars	0.064	
Bushehr	0.067	
Semnan	0.075	
Isfahan	0.077	
Qazvin	0.078	
Yazd	0.085	
Khuzestan	0.089	
Kohkiluye Buyerahmad	0.096	
Chaharmahal Bakhtiari	0.106	
Ilam	0.110	Group 2
Zanjan	0.117	
Markazi	0.131	
Qom	0.137	
Hormozgan	0.139	
Tehran	0.142	
Kermanshah	0.150	
Kerman	0.152	
Mazandaran	0.161	
Hamedan	0.162	
Khorasan South	0.164	
Lorestan	0.177	
Alborz	0.180	
Azarbaijan East	0.188	
Kurdistan	0.201	
Khorasan Razavi	0.213	
Khorasan North	0.219	
Azarbaijan West	0.224	
Ardebil	0.246	Group 3
Golestan	0.275	
Sistan Baluchestan	0.448	

Abbreviation: HBs Ag, Hepatitis B Surface Antigen.

Monte Carlo simulation method was used to compute

95% uncertainty range for estimated national prevalence. Two sources of uncertainty were considered in Monte Carlo simulation. The first source of uncertainty was in extrapolating prevalence estimate in each stratum. In each simulation, the prevalence in each province was extracted from a normal distribution with the mean and standard error of the pooled prevalence estimate in the corresponding stratum. The second source of uncertainty was in the estimated number of people with HBs Ag positive in each simulation given the prevalence estimates obtained from the described normal distribution. A Poisson distribution was set on the number of people with HBs Ag positive in each province. A total of 10,000 simulations were computed for estimated national prevalence of HBs Ag while the percentiles 2.5 and 97.5 were considered as the lower and upper bounds of uncertainty range.

Method 2 was not used for estimating anti-HBc Ab prevalence given that the data of anti-HBc Ab prevalence among blood donors were not available.

All the analyses were conducted using Microsoft Excel 2010 (Microsoft©, Redmond, WA, USA) and Stata 14.0 (StataCorp, College Station, Texas, USA).

3. Results

3.1. Study Selection

The studies included and excluded through the review process were summarized in Figure 1. A total of 5,381 records were found in the initial search; 4,085 records were screened by title and abstract; 63 full-text articles were reviewed, and 13 studies included in the analysis (Figure 1).

3.2. Study Characteristics

The characteristics of the included studies were summarized in Table 2. Thirteen studies from 12 provinces were included (2-10, 17-20). In 12 studies (2-8, 10, 17-20), each study was conducted in a single province while one study (9) covered three provinces. All studies assessed HBs Ag while nine studies assessed anti-HBc Ab (Table 2). In 12/13 of studies assessing HBs Ag, and in 6/9 of studies assessing anti-HBc Ab, gender-specific prevalence data were available in the paper or by contacting the authors (Table 2). All included studies measured HBs Ag and anti-HBc Ab using enzyme-linked immunosorbent assay (ELISA).

3.3. Risk of Bias Assessment

The results of the critical appraisal of included studies were summarised in Supplementary file appendix 2. Eleven studies were identified as having a low risk of bias (quality assessment score > 7).

3.4. Results of Individual Studies

The prevalence of HBs Ag and anti-HBc Ab, reported in the individual studies were illustrated in Figures 2 and 3, respectively.

The prevalence of HBs Ag was highly heterogeneous across studies (I-square = 91.7%), from 0.76% in Kermanshah to 5.10% in Golestan (Figure 2A). In most studies, prevalence was higher among men than women (Figure 2B and C).

Temporal variation in HBs Ag prevalence could be assessed in three provinces, including Hormozgan, Khorasan Razavi, and Sistan Baluchestan given that two studies in different time points were available in each of these provinces. In Hormozgan, HBs Ag prevalence decreased from 2.70% (95% CI: 1.88%, 3.52%) in 2006, to 1.52% (95%CI: 1.14%, 1.89%) in 2008 - 09. The 95%CIs were marginally overlapped. In the two other provinces, the time differences between two studies were narrower with more evident overlaps between 95%CIs. In Khorasan Razavi, HBs Ag prevalence decreased from 2.00% (95% CI: 1.31%, 3.01%) in 2009 to 1.57% (95% CI: 0.81%, 2.33%) in 2010 - 11. In Sistan Baluchestan, HBs Ag prevalence increased from 3.19% (95% CI: 2.26%, 4.12%) in 2008 - 09 to 3.81% (95% CI: 2.94%, 4.69%) in 2010.

Similarly, the prevalence of anti-HBc Ab was also highly heterogeneous across studies (I-square = 99.3%), ranging 4.17% in Isfahan to 36.90% in Golestan (Figure 3A). The prevalence among men was higher than women in all studies (Figure 3C, and C). There was only one study available for each province.

3.5. Synthesis of Results

The estimated national prevalence of HBs Ag and anti-HBc Ab were summarised in Table 3. Using method 1, the national prevalence of HBs Ag was estimated as 1.84% (95%CI: 1.61%, 2.09%). The estimated prevalence was significantly higher among men (2.36%; 95%CI: 1.97%, 2.83%) than women (1.47%; 95%CI: 1.21%, 1.78%). The national prevalence of anti-HBc Ab was estimated as 13.59% (95%CI: 12.92%, 14.29%), with a significantly higher prevalence in men (15.21%; 95%CI: 14.08%, 16.41%), than women (12.77%; 95%CI: 11.87%, 13.72%).

In a sensitivity analysis, including only 11 studies with a low risk of bias (quality assessment score > 7), HBs Ag prevalence was estimated as 1.95% (95%CI: 1.71%, 2.22%), and anti-HBc Ab prevalence was estimated as 15.51% (95%CI: 14.76%, 16.29%; Supplementary file appendix 3.

Using method 2, the national prevalence of HBs Ag was estimated as 1.79% (95% uncertainty range: 1.67%, 1.91%) which is slightly lower than the estimate obtained by using method 1. The estimated prevalence was higher among men (2.24%; range: 2.15%, 2.59%) than women (1.42%; range: 1.28%, 1.56%). Based on the estimated prevalence by

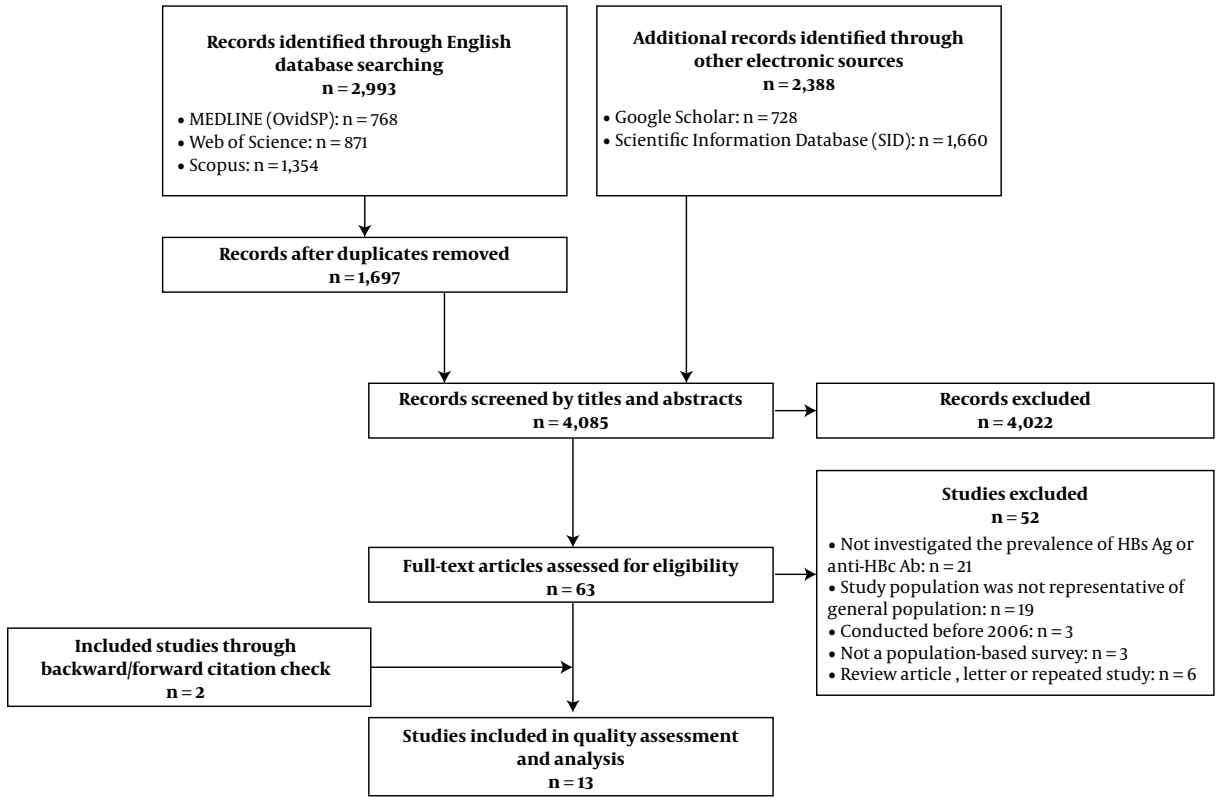


Figure 1. Flow Diagram Detailing Review Process and study selection

method 2, it was estimated that there are 1,347,000 (range: 1,253,000 - 1,434,000) individuals living with chronic HBV infection in Iran, including 900,000 (range: 815,000 - 982,000) men and 529,000 (range: 477,000 - 581,000) women.

The actual burden of HBV infection in the provinces with available study was illustrated in Figure 4. This shows Figure that among 12 studied provinces, Tehran, Golestan, Sistan Baluchestan, Khorasan Razavi and Isfahan have the highest absolute number of individuals with HBV infection. It also shows that although some provinces such as Khorasan Razavi or Isfahan have low HBs Ag prevalence, the burden of HBV infection in these provinces is still high, primarily because of the large population size of the province.

4. Discussion

The current study estimated the prevalence of HBs Ag in the Iranian general population as 1.79% (1.67% to 2.32%), equating to 1,347,000 (1,253,000 to 1,434,000) individuals living with chronic HBV infection in Iran. The prevalence of anti-HBc Ab was estimated as 13.59% (12.92% to 14.29%).

This study was conducted given the lack of a national survey in the recent years to provide the best available national estimates of HBs Ag and anti-HBc Ab prevalence in Iran. Two methods were used in the current study to estimate the national HBs Ag prevalence. The outputs of two methods are close, indicating a robustness of the methods used.

The previous estimate of HBs Ag prevalence in Iran was 2.14% during 2001 - 06 (12), which was higher than the current estimate. Although potent antiviral treatments are available for HBV infection, the rate of HBs Ag seroconversion is very low. The reduction in HBs Ag prevalence in Iran could be primarily due to a reduced HBV incidence related to the high coverage of universal infant HBV vaccination program, implemented since 1993 (21), and adolescents HBV vaccination campaigns, implemented in 2007 - 2010 (22, 23). The impact of Iranian universal infant vaccination program on decreasing HBs Ag prevalence was demonstrated in a study identifying a marked reduction among children 2 - 14 years old, from 1.3% in 1991, two years before initiation of the program, to 0.8% in 1999, six years after initiation of the program (11). Further studies with a

Table 2. Characteristics of the Studies Investigating Prevalence of HBs Ag or anti-HBc Ab in General Population, Included in the Analysis

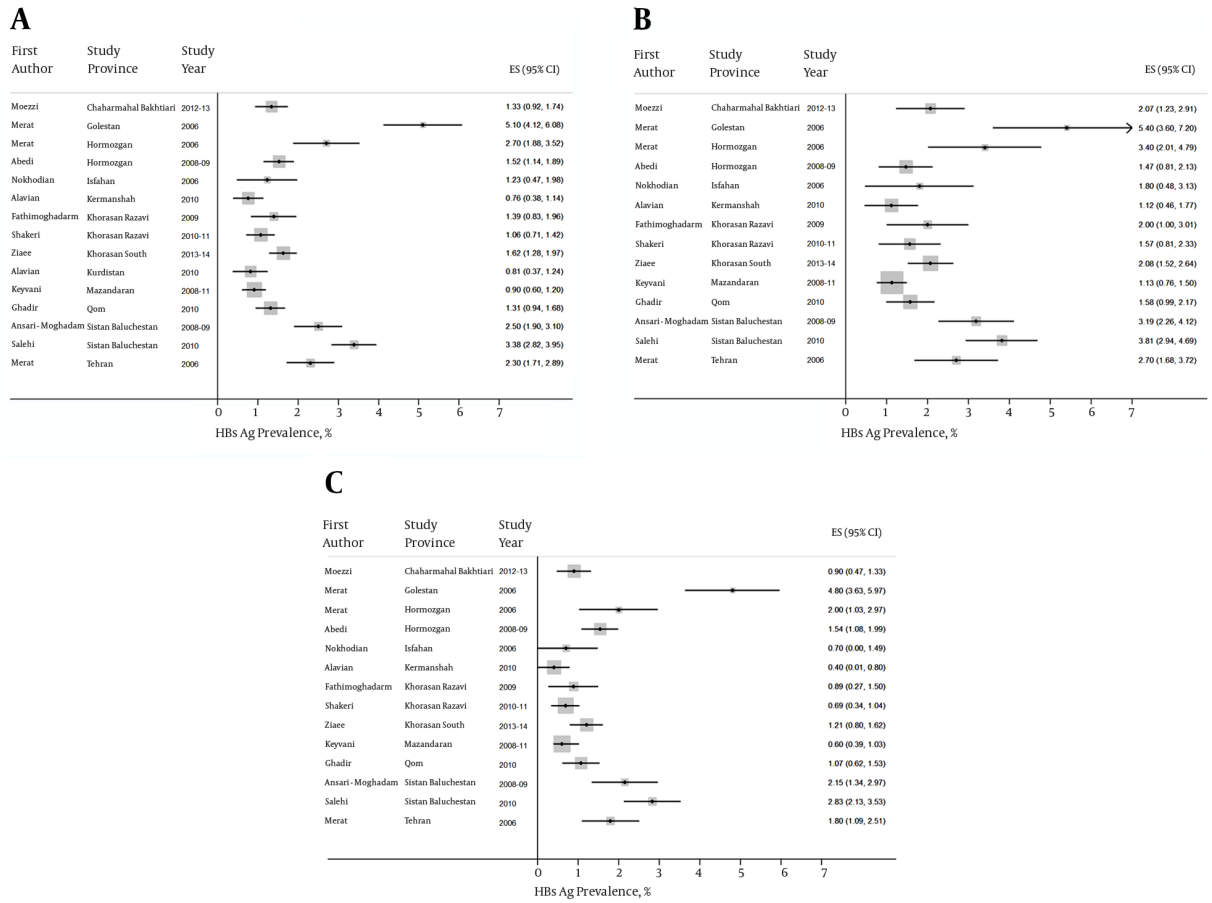
First Author	Study Year	Study Province	Study City	Sampling Method	Study Population Size, No.	Study Population Gender Ratio, Number of Men per 100 Women	Study Population Age Restriction, y	HBV Markers Measured, HBs Ag, anti-HBc Ab
Moezzi	2012 - 13	Chaharmahal Bakhtiari	All cities	Cluster sampling (one-stage)	3,000	59	≥ 15	HBs Ag[a]
Merat	2006	Golestan	All cities	Cluster sampling (one-stage)	1,896	47	18 - 65	HBs Ag[a], anti-HBc Ab[a]
Merat	2006	Hormozgan	All cities	Cluster sampling (one-stage)	1,455	82	18 - 65	HBs Ag[a], anti-HBc Ab[a]
Abedi	2008 - 09	Hormozgan	All cities	Cluster sampling (multi-stage)	4,087	46	8 - 80	HBs Ag[a], anti-HBc Ab
Nokhodian	2006	Isfahan	All cities	Cluster sampling (multi-stage)	816	91	> 6	HBs Ag[a], anti-HBc Ab[a]
Alavian	2010	Kermanshah	All cities	Cluster sampling (one-stage)	1,979	99	6 - 65	HBs Ag[a], anti-HBc Ab[a]
Fathimoghadam	2009	Khorasan Razavi	Mashhahd	Cluster sampling (multi-stage)	1,652	83	1 - 90	HBs Ag[a]
Shakeri	2010 - 11	Khorasan Razavi	Mashhahd	Cluster sampling (multi-stage)	3,198	47	Not Defined[b]	HBs Ag[a]
Ziaee	2013 - 14	Khorasan South	Birjand	Cluster sampling (one-stage)	5,235	92	15 - 70	HBs Ag[a], anti-HBc Ab[a]
Alavian	2010	Kurdistan	All cities	Cluster sampling (one-stage)	1,613	51	6 - 65	HBs Ag, anti-HBc Ab
Keyvani	2008 - 11	Mazandaran	Amol	Cluster sampling (one-stage)	6,146	130	> 10	HBs Ag[a], anti-HBc Ab[a]
Ghadir	2010	Qom	All cities	Cluster sampling	3,666	87	Not Defined	HBs Ag[a]
Salehi	2010	Sistan Baluchestan	All cities	Cluster sampling (one-stage)	3,989	85	6 - 65	HBs Ag[a], anti-HBc Ab[a]
Ansari-Moghadam	2008 - 09	Sistan Baluchestan	Zahedan	Cluster sampling (multi-stage)	2,587	114	> 10	HBs Ag[a], anti-HBc Ab
Merat	2006	Tehran	All cities	Cluster sampling (one-stage)	2,327	71	18 - 65	HBs Ag[a], anti-HBc Ab[a]

Abbreviations: HBs Ag, Hepatitis B Surface Antigen; anti-HBc Ab, Hepatitis B Core Antibody.
[a] Gender-specific prevalence data were available.
[b] Age range of the recruited study population: 15 - 65 years.

specific focus on age cohorts covered in the adolescent HBV vaccination campaigns are required to assess the impact of the campaigns on HBV prevalence.

The current study showed that the risk of HBV infection varies widely across provinces. Although a reduction in national prevalence of HBs Ag was observed, there are still

Figure 2. Forest Plots of Studies, Investigating the Prevalence of HBs Ag in General Population Among Both Genders (A), Men (B), and Women (C)

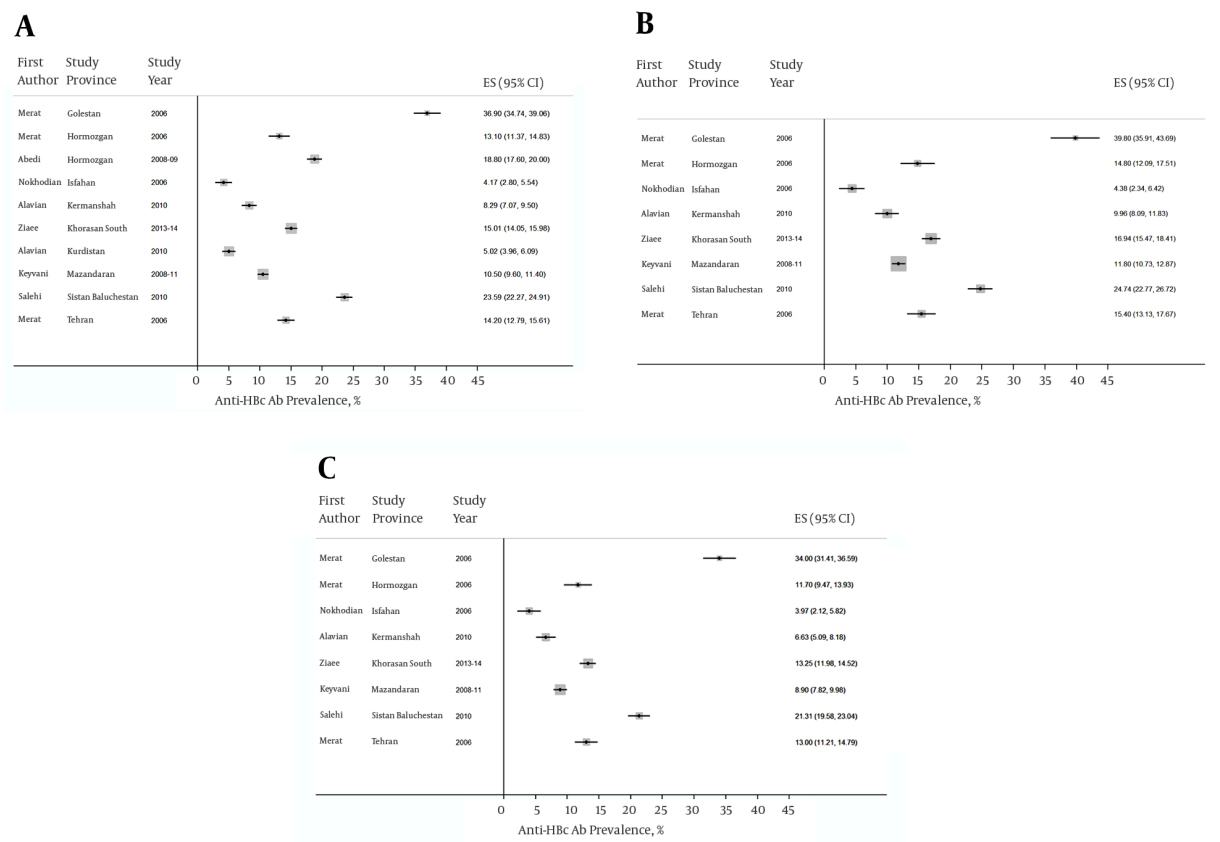


I-square was 91.7%, 82.1%, and 88.0% among studies on both genders, men, and women, respectively.

provinces with high prevalence. Some studies included in the current analysis also showed a marked within-province heterogeneity in HBV risk (4, 10). In Sistan Baluchestan the prevalence of HBs Ag varied from zero to about 5% in different cities (4), while in Kermanshah, a low-prevalence province, the prevalence varied from zero to 3.8% (10). This heterogeneous pattern of HBV infection distribution suggested that HBV control strategies need to be localised, considering the HBV epidemic in each province/city.

Golestan and Sistan Baluchestan were two provinces with the highest prevalence of HBs Ag and anti-HBc Ab. In Golestan, one study reported an HBsAg prevalence of 5.1% in people 18 - 65 years old (9), while in a more recent study recruiting an older cohort (40 - 75 years) the prevalence was 7% (24). In both studies, prevalence was higher among men than women. In Sistan Baluchestan, the prevalence of HBs Ag was comparable between men and women while age was demonstrated as an important predictor of HBV risk, with HBs Ag prevalence increasing from 0.4% among people < 18 years old to 5.7% among those > 65 years old (5). This high prevalence of HBs Ag in adults, particularly in women indicates the importance of interventions to prevent mother-to-child transmission, including birth-dose vaccination and immunoglobulin. Further studies on the coverage and effectiveness of currently implemented prevention strategies are needed in these provinces. Another study in Golestan among children of HBV infected parents, 10 - 18 years after their primary neonatal vaccination, showed that 70% of participants had anti-HBs Ab < 10 IU/mL. After receiving HBV vaccine booster, 20% of them had no anamnestic response, with a higher proportion among older individuals, suggesting a waning of immune memory in some of the children/adolescents who will be at risk of horizontal transmission (25). More research of intra-familiar horizontal transmission is required, particularly in provinces where HBV is endemic.

Figure 3. Forest Plot of Studies, Investigating the Prevalence of anti-HBc Ab in General Population, Among Both Genders (A), Men (B), and Women (C)



I-square was 99.3%, 98.3%, and 98.7% among studies on both genders, men, and women, respectively.

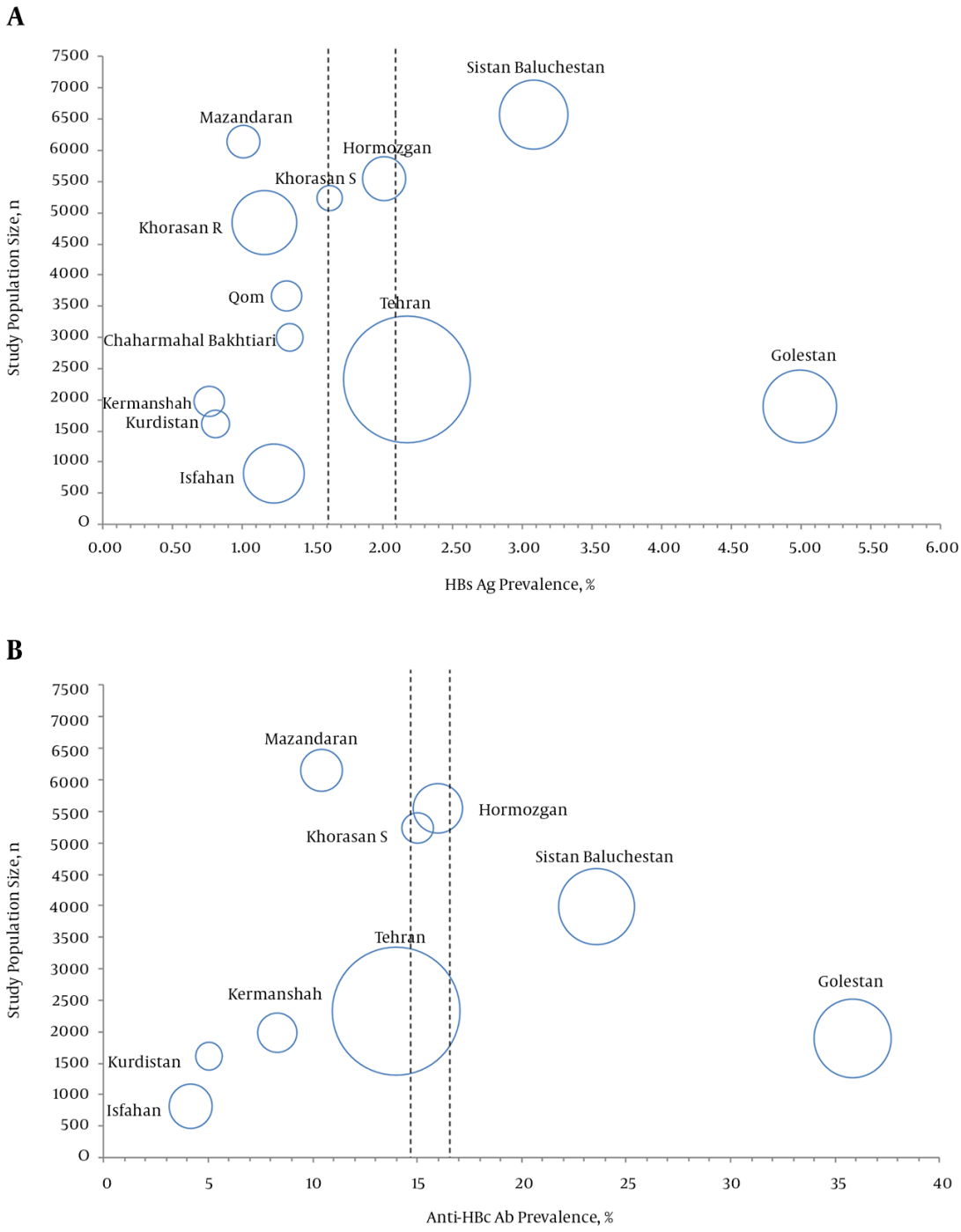
The current study has introduced a sophisticated methodology to use provincial data to provide the best available estimate of national prevalence of HBV infection and exposure. However, this study had several limitations. Data from several provinces was unavailable. HBs Ag prevalence data among blood donors were used to overcome this limitation but there are still remaining concerns about publication bias and uncertainties about the estimated prevalence in the provinces with no available survey data. This is particularly important given that the risk ratio of HBV infection among the general population to that in blood donors were not consistent across provinces. The prevalence estimates reported in this study can be updated whenever more provincial data are made available. The number of studies included in this analysis did not provide sufficient statistical power to assess the source of heterogeneity and also the temporal trend in HBV prevalence in the national level. Google Scholar was used to search grey literature, thus the documents not covered by Google Scholar have not been included in this study. The cut-off in HBs Ag prevalence in blood donors, used for classifying the provinces were based on expert opinion.

In conclusion, this study indicated that the prevalence of HBs Ag in Iran has decreased over the last decade, although there are provinces that still experience a high prevalence. More detailed data of the epidemiological profile of HBV infection and HBV transmission in provinces with a higher prevalence is required, including age-specific prevalence data, coverage and effectiveness of mother-to-child transmission prevention interventions, and intra-familiar horizontal HBV transmission. These data can help in designing appropriate interventions to control HBV transmission in provinces where HBV infection is endemic.

Supplementary Material

Supplementary material(s) is available here.

Figure 4. Heterogeneity of the Estimated Prevalence and Burden of HBs Ag (A) and anti-HBc Ab (B) in Studied Provinces in Iran.



The bobbles sizes are based on the estimated number of people living with HBs Ag or anti-HBc Ab in each province. The vertical dotted lines represent the 95% confidence interval of the estimated national prevalence of HBs Ag or anti-HBc Ab (method 1).

Table 3. Estimated National Prevalence of HBs Ag and anti-HBc Ab in General Population

Variables	Gender	Prevalence (%)	95% Confidence Interval (%)
Method 1			
HBs Ag	Both genders	1.84	1.61, 2.09
HBs Ag	Men	2.36	1.97, 2.83
HBs Ag	Women	1.47	1.21, 1.78
Anti-HBc Ab	Both genders	13.59	12.92, 14.29
Anti-HBc Ab	Men	15.21	14.08, 16.41
Anti-HBc Ab	Women	12.77	11.87, 13.72
Method 2			
HBs Ag	Both genders	1.79	1.67, 1.91
HBs Ag	Men	2.24	2.15, 2.59
HBs Ag	Women	1.42	1.28, 1.56

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References

1. World Health Organization . Combating hepatitis B and C to reach elimination by 2030. Geneva, Switzerland: World Health Organization; May 2016.
2. Ziaee M, Ebrahimzadeh A, Azarkar Z, Namaei MH, Saburi A, Fereidouni M, et al. Seroprevalence and Risk Factors for Hepatitis B in an Adult Population: The First Report from Birjand, South Khorasan, Iran. *Hepat Mon.* 2016;**16**(9):e36452. doi: 10.5812/hepatmon.36452. [PubMed: 27822260].
3. Keyvani H, Sohrabi M, Zamani F, Poustchi H, Ashrafi H, Saeedian F, et al. A population based study on hepatitis B virus in northern iran, amol. *Hepat Mon.* 2014;**14**(8):e20540. doi: 10.5812/hepatmon.20540. [PubMed: 25237372].
4. Salehi M, Alavian SM, Tabatabaei SV, Izadi S, Sanei Moghaddam E, Amini Kafi-Abad S, et al. Seroepidemiology of HBV infection in South-East of iran; a population based study. *Iran Red Crescent Med J.* 2012;**14**(5):283–8. [PubMed: 22829987].
5. Ansari-Moghaddam A, Ostovaneh MR, Sharifi Mood B, Sanei-Moghaddam E, Modabbernia A, Poustchi H. Seroprevalence of hepatitis B surface antigen and anti hepatitis C antibody in zahedan city, iran: a population-based study. *Hepat Mon.* 2012;**12**(9):e6618. doi: 10.5812/hepatmon.6618. [PubMed: 23087764].
6. Alavian SM, Tabatabaei SV, Ghadimi T, Beedrapour F, Kafi-Abad SA, Gharehbaghian A, et al. Seroprevalence of Hepatitis B Virus Infection and Its Risk Factors in the West of Iran: A Population-based Study. *Int J Prev Med.* 2012;**3**(11):770–5. [PubMed: 23189228].
7. Abedi F, Madani H, Asadi A, Nejatizadeh A. Significance of blood-related high-risk behaviors and horizontal transmission of hepatitis B virus in Iran. *Arch Virol.* 2011;**156**(4):629–35. doi: 10.1007/s00705-010-0902-y. [PubMed: 21229276].
8. Ataei B, Nokhodian Z, Javadi AA, Kassaian N, Shoaei P, Farajzadegan Z, et al. Hepatitis E virus in Isfahan Province: a population-based study. *Int J Infect Dis.* 2009;**13**(1):67–71. doi: 10.1016/j.ijid.2008.03.030.
9. Merat S, Rezvan H, Nouraie M, Jamali A, Assari S, Abolghasemi H, et al. The prevalence of hepatitis B surface antigen and anti-hepatitis B core antibody in Iran: a population-based study. *Arch Iran Med.* 2009;**12**(3):225–31. [PubMed: 19400598].
10. Alavian SM, Tabatabaei SV, Nourizad S, Mansouri F, Khademi N, Amini Kafi-abad S, et al. Seroepidemiology of HBV Infection in Kermanshah-West of Iran; a Population Based Study. *Jundishapur J Microbiol.* 2012;**5**(4):564–9. doi: 10.5812/jjm.4156.
11. Zali MR, Mohammad K, Noorbala AA, Noorimayer B, Shahraz S. Rate of hepatitis B seropositivity following mass vaccination in the Islamic Republic of Iran. *East Mediterr Health J.* 2005;**11**(1-2):62–7. [PubMed: 16532672].
12. Alavian SM, Hajarizadeh B, Ahmadzad-Asl M, Kabir A, Bagheri-Lankarani K. Hepatitis B virus infection in Iran: A systematic review. *Hepatitis Mon.* 2008;**8**(4):281–94.
13. Mohammadi Z, Keshtkar A, Eghtesad S, Jeddian A, Pourfatholah AA, Maghsudlu M, et al. Epidemiological Profile of Hepatitis B Virus Infection in Iran in the Past 25 years; A Systematic Review and Meta-analysis of General Population Studies. *Middle East J Dig Dis.* 2016;**8**(1):5–18. doi: 10.15171/mejdd.2016.01. [PubMed: 26933476].
14. Salehi-Vaziri M, Sadeghi F, Almasi Hashiani A, Gholami Fesharaki M, Alavian SM. Hepatitis B Virus Infection in the General Population of Iran: An Updated Systematic Review and Meta-Analysis. *Hepat Mon.* 2016;**16**(4):e35577. doi: 10.5812/hepatmon.35577. [PubMed: 27257428].
15. Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group . Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* 2009;**151**(4):264–9. doi: 10.7326/0003-4819-151-4-200908180-00135. [PubMed: 19622511] W64.
16. Munn Z, Moola S, Riitano D, Lisy K. The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. *Int J Health Policy Manag.* 2014;**3**(3):123–8. doi: 10.15171/ijhpm.2014.71. [PubMed: 25197676].
17. Moezzi M, Imani R, Khosravi N, Pourheidar B, Ganji F, Karimi A. Hepatitis B seroprevalence and risk factors in adult population of chaharmahal and bakhtiari province in 2013. *Hepat Mon.* 2014;**14**(5):e17398. doi: 10.5812/hepatmon.17389. [PubMed: 24910705].
18. Shakeri MT, Foghanian B, Nomani H, Ghayour-Mobarhan M, Nabavinia MS, Rostami S, et al. The prevalence of hepatitis B virus infection in mashhad, iran: a population-based study. *Iran Red Crescent Med J.* 2013;**15**(3):245–8. doi: 10.5812/ircmj.8200. [PubMed: 23984006].
19. Ghadir MR, Belbasi M, Heidari A, Jandagh M, Ahmadi I, Habibinejad H, et al. Distribution and risk factors of hepatitis B virus infection in the general population of Central Iran. *Hepat Mon.* 2012;**12**(2):112–7. doi: 10.5812/hepatmon.822. [PubMed: 22509188].
20. Fathimoghaddam F, Hedayati-Moghaddam MR, Bidkhori HR, Ahmadi S, Sima HR. The prevalence of hepatitis B antigen-positivity in the general population of Mashhad, Iran. *Hepat Mon.* 2011;**11**(5):346–50. [PubMed: 22087159].
21. Esteghamati A, Keshtkar AA, Nadjafi L, Gouya MM, Salaramoli M, Roshandel G, et al. Hepatitis B vaccination coverage among Iranian children aged 15-26 months in 2006. *East Mediterr Health J.* 2011;**17**(2):93–100. [PubMed: 21735942].
22. Alavian SM, Zamiri N, Gooya MM, Tehrani A, Heydari ST, Lankarani KB. Hepatitis B vaccination of adolescents: a report on the national program in Iran. *J Public Health Policy.* 2010;**31**(4):478–93. doi: 10.1057/jphp.2010.35. [PubMed: 21119653].

23. Alavian SM, Gooya MM, Hajarizadeh B, Esteghamati AR, Moeinzadeh AM, Haghazali M. Mass vaccination campaign against hepatitis B in adolescents in Iran. Estimating coverage using administrative data. *Hepatitis Mon.* 2009;**9**(3):189–95.
24. Poustchi H, Katoonizadeh A, Ostovaneh MR, Moossavi S, Sharafkhah M, Esmaili S, et al. Cohort profile: golestan hepatitis B cohort study-a prospective long term study in northern iran. *Middle East J Dig Dis.* 2014;**6**(4):186–94. [PubMed: 25349681].
25. Katoonizadeh A, Sharafkhah M, Ostovaneh MR, Norouzi A, Khoshbakht N, Mohamadkhani A, et al. Immune responses to hepatitis B immunization 10-18 years after primary vaccination: a population-based cohort study. *J Viral Hepat.* 2016;**23**(10):805–11. doi: 10.1111/jvh.12543. [PubMed: 27126365].