

REVIEW  
ARTICLE

## Hepatitis B Virus Infection in Iran: A Systematic Review

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**Background and Aims:** Hepatitis B virus (HBV) infection is a worldwide problem. It is estimated that 400 million people are suffering from this infection. We conducted a systematic review to put all evidence on HBV infection in I.R. Iran and to make an accurate estimate of HBV infection prevalence in Iran for further planning to control the infection.

**Study Design:** Meta-analysis and survey data analysis of all national and international papers, theses, congresses, reports, Iranian medical universities projects, research centers, reports of Deputy for Health affairs (published or unpublished).

**Setting & Population:** Iranian general population with positive HBsAg in blood samples

**Selection Criteria for Studies:** All descriptive/analytical cross-sectional studies/surveys from April 2001 to March 2007 that have sufficiently declared objectives, proper sampling method with identical and valid measurement instruments for all study subjects and proper analysis methods regarding sampling design and demographic adjustments

**Outcomes:** Presence of positive HBsAg in blood samples of study samples

**Results:** Fourteen studies met the inclusion criteria. They were from 7 (out of 30) provinces in which about 40 percent of the country population live. These provinces (HBsAg positive prevalence) were Golestan (6.3%), Tehran (2.2%), East Azarbaijan (1.3%), Hamedan (2.3%), Isfahan (1.3%), Kermanshah (1.3%) and Hormozgan (2.4%). The HBV infection prevalence in Iran is estimated to be 2.14 percent (95%CI: 1.92-2.35), in men and women 2.55 percent (95%CI: 2.25-2.85) and 2.03 percent (95%CI: 1.6-2.46 percent) respectively.

**Conclusions:** About 1.5 million people in Iran are living with HBV infection (mild to moderate prevalence according to WHO classification) and it is assumed that 15% to 40% of them are at risk of developing cirrhosis and/or hepatocellular carcinoma (HCC) without intervention. The prevalence of HBV infection has been reported higher in more recent studies compared to the study in 2000-2001.

**Keywords:** Hepatitis B, Iran, Systematic Review

## Introduction

Hepatitis B virus (HBV) infection is a worldwide problem and between 350 and 400 million persons are estimated to suffer from this infection <sup>(1)</sup>. HBV infection is a contagious disease that may transmit vertically from mothers to their neonates or horizontally by means of blood products and body secretions.

The first published report about HBV infection in Iran was in 1972 <sup>(2)</sup>. In later studies, the rate of HBV infection was reported from 1% to 2.1% in 1977 <sup>(3)</sup> while further reports stated higher rates (between 3.5% <sup>(4)</sup> and 2.49% <sup>(5)</sup>) in both voluntary blood donors and general population <sup>(4)</sup> from 1988 to 1993. In Islamic Republic of Iran (I.R. Iran) mass

vaccination of neonates against HBV infection started from 1993 as a national program in routine neonates care. This program is supposed to affect the prevalence rate of HBV infection thorough the

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country and decrease the rate of infection after a while (6, 7). More recent studies reported the range of HBV infection between 1.2 (8) to 9.7 (9) percent in different regions of the country. Generally, it is estimated that about 1.5 to 2.5 million people are suffering from HBV infection in I.R. Iran, and some of them are carriers that may transmit infection to others unintentionally (6, 10, 11). One of the most effective programs in reducing the rate of HBV infection is decreasing carriers' pool in the community which could be achieved by vaccination programs. This, or any other effective program, needs more accurate estimates of the prevalence of HBV infection in the country (10). The changing epidemiology of HBV infection in the world and in Iran is a result of global and mass vaccination programs in high risk and susceptible groups (7).

We conducted a systematic review to put all evidence on HBV infection in I.R. Iran and to make an accurate estimate of HBV infection prevalence in Iran for further planning to control the infection. This study would also determine the endemicity status (high, intermediate or low) of HBV infection in Iran.

## Methods

We studied the prevalence of HBV in Iran through a comprehensive systematic review of literature, evidences followed by Survey data analysis

and meta-analysis of findings to estimate the prevalence of HBV infection in Iranian general population.

### Study question

The populations of interest was Iranian general population and the interested outcome was presence of positive HBsAg in blood samples of the study population, based on any blood tests such as enzyme-linked immuno-sorbent assay (ELISA) or even if laboratory tests are not identified clearly, from April 2001 to March 2007.

### Search strategy

The search strategy was based on study question (Table 1) for electronic searches and hand searching, performed for MeSH term "Hepatitis B", "HBV" and "Iran" key words in titles and/or abstracts.

### Electronic databases

We searched 12 electronic databases of biological sciences and health including Medline (Pubmed), EMBase, Scopus, ISI, CABI, CINAHL, DOAJ, Index Medicus for Eastern Mediterranean Region-IMEMR, EMROMedex, High-wire press, Cochrane library and DARE. And also three national databases of medical and life sciences literature were searched including Scientific Information Database (SID), Iranmedex and Magiran. The Iranian health sciences journals that are not indexed in electronic databases,

**Table 1.** Estimations of HBV infection prevalence in I.R. Iran and its provinces between 2001 and 2007.

Province	Study's First Author (Year)	Study(ies) target population	Total Sample Size(s)	Province Population	Weight*	Total; % (95%CI)	Men; % (95%CI)	Women; % (95%CI)
E.Azarbaijan	Bayat-Makou (2001), Mahabadi(2004-5), Montazam(2004)	G.P. Married people Adults&children	5320	3,603,456	677.34	1.3 (1.0-1.6)	1.7 (1.2-2.1)	0.8 (0.1-1.5)
Golestan	Pourshams(2003), Abdolahi(2004), Poorshams(2007)	G.P. G.P. G.P.	4931	1,617,087	327.94	6.3 (3.2-9.3)	7.3 (3.9-10.7)	5.4 (2.7-8.2)
Hamedan	Alizadeh(2003)	G.P.	1824	1,703,267	933.81	2.3 (1.6-3.0)	2.2 (1.3-3.2)	2.4 (1.3-3.4)
Hormozgan	Merat(2006)	G.P.	1988	1,403,674	706.07	2.4 (1.6-3.1)	3.1 (2.0-4.2)	1.8 (1.0-2.6)
Isfahan	Ataie(2006)	G.P.	816	4,559,256	5587.32	1.3 (0.5-2.1)	N.D.***	N.D.
Kermanshah	Kazerani(1999-2003)	Patients on surgery	6820	1,879,385	275.57	1.3 (1.0-1.6)	N.D.	N.D.
Tehran	Pourshams(2001), Hasanpour(2001-2), Parsania(2003-5), Merat(2007)	Students Patients on surgery Patients on surgery G.P.	7870	13,422,366	1705.51	2.2 (1.9-2.5)	2.2 (1.7-2.6)	1.9 (1.2-2.6)
National	N.A.**	N.A.	N.A	70,495,782	N.A.	2.14 (1.9-2.35)	2.55 (2.25-2.85)	2.03 (1.6-2.46)

\* Weight= Province population/Total sample size,

\*\*N.A.: Not Applicable.

\*\*\* ND.: Not Determined. G.P.: General population

49 journals, were searched manually in search time period. So the study covered all registered and certified life sciences and medical journal in national level.

### Gray literature search

Gray literature search was performed as below: There were 431 national, regional and international medical sciences congresses and seminars that were held in the study time period in Iran and we selected and hand searched 45 out of 48 relevant congresses and seminars abstract books by two independent reviewers. The research projects of 27 out of 40 universities of medical sciences in Iran were also searched from their internet web sites. We also searched national reports from Center for Diseases Control-CDC- of Iran Ministry of Health and Iran Blood Transfusion organization -IBTO-in the study time period. Medical sciences students' thesis searches were also performed by two independent reviewers from Iranian center for scientific documents and records; IranDoc. Finally, we consulted with two experts in HBV researches in Iran (Prof. Reza Malekzadeh and Prof. Seyed Moayed Alavian) and searched their personal archives for more additional citations.

Forward citation and backward citation of searched citations were performed.

### Critical appraisal and selection of studies

We reviewed all citations thoroughly by two independent reviewers and checked for eligibility criteria to include the studies in the analysis. The inclusion criteria were all descriptive/analytical cross-sectional studies/surveys that have specified temporal and geographic specifications of the study, sufficiently declared objectives, proper sampling methods that could generalize findings to target population with identical and valid measurement instruments for all study subjects and proper analysis methods regarding sampling design and demographic adjustments. We revised the criteria developed by Sharifi *et al.* for this purpose<sup>(12)</sup>.

### Data extractio

The selected and included citations were reviewed and the findings were extracted to excel spreadsheets, the extracted data were year of the study, first author, province and district of the study, sample population, sampling method, sample size, HBsAg detection method, HBsAg kit name, Age mean and standard error (SE) of subjects, percent of male subject, HBV point prevalence in study subjects and in males/females and SE. If there were other parameters reported other than SE, such as standard deviation,

confidence interval, and/or P.value, the proper modifications were performed to calculate SE.

### Analysis

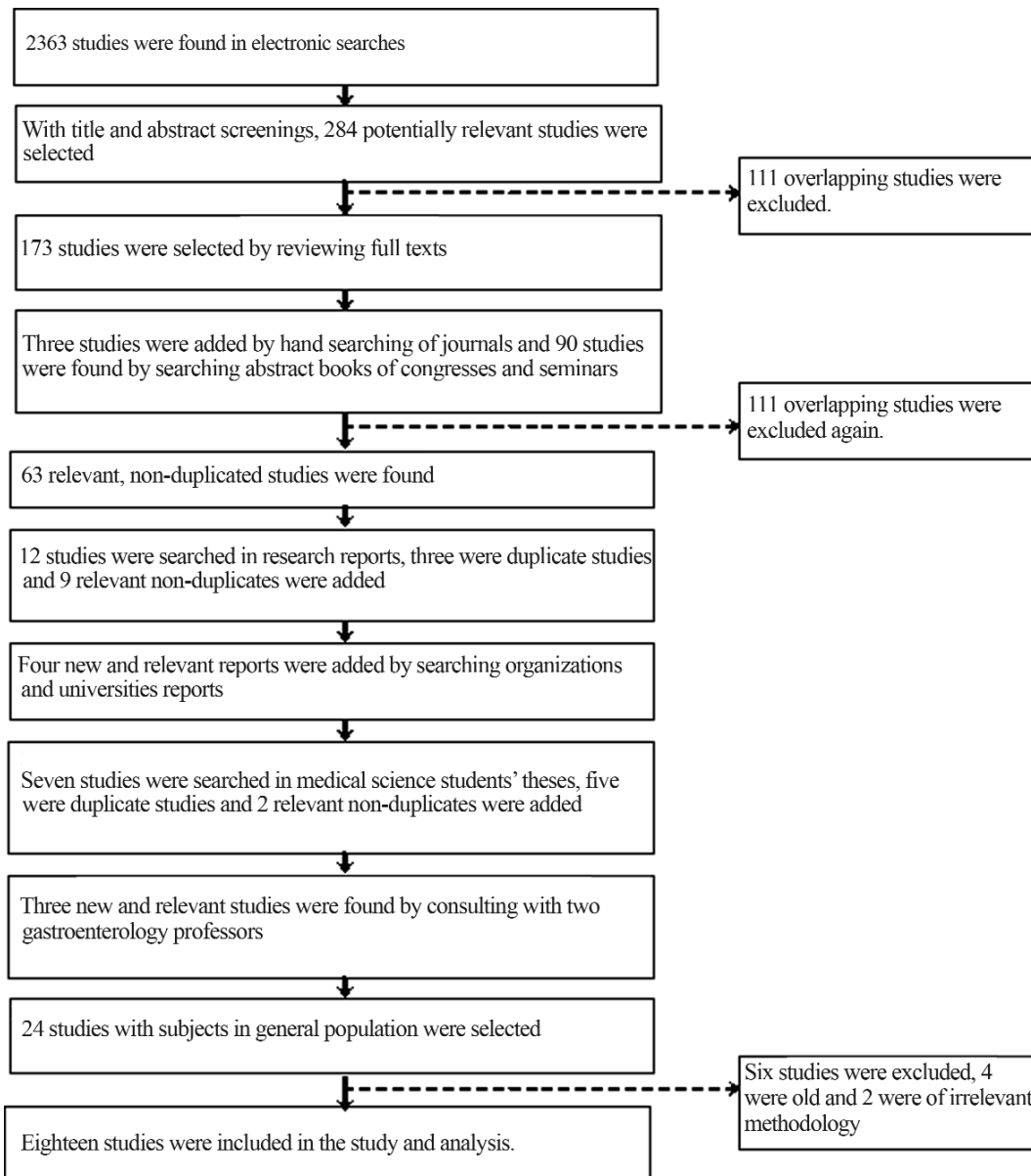
The extracted data were analyzed to estimate point prevalence of HBV infection and its 95% confidence interval (CI). Statistical heterogeneity of results was checked using Cochran Q-test with significance set at  $P < 0.1$ . We used meta-analysis method with "meta" command using fix/random model based on the results of heterogeneity test. The results were showed in geographic maps using ArcView 3.2a software (ESRI Inc. NY). We also pooled studies from each province using meta-analysis methods to estimate the prevalence of HBV in that province. We also considered survey data analysis methods to estimate more accurate HBV infection prevalence in our country. It seems that meta-analysis methods would not be suitable methods to achieve the objectives of this systematic review; because in the meta-analysis methods, weight of studies is based on their sample sizes not the population size of the provinces that those studies were from. Considering that the population of the 7 provinces that we found studies from is 28,188,491 people based on 2006 national census (about 40 percent of the country population), we used survey data analysis method to calculate nationwide prevalence estimate considering weight of each province as province population to sample size(s) ratio. The analysis was performed in STATA 9 software (STATA Corp. LP).

## Results

### Search result

We found 173 relevant citations out of all 2363 searched citations<sup>(2-168)</sup> where 62 studies were not overlapping studies (duplicate studies found by several search routes) in electronic search. In gray literature search another 191 studies were found where 85 citations out of 191 were selected<sup>(155, 167-214)(142, 215-250)</sup>. No new results were produced from backward citation and forward citation of found studies.

After excluding overlapping reports to avoid double counting, overlapping samples and studies with target populations that were not representative of general population, we finally selected 24 studies with subjects in general population, out of which 4 were crossed out because they were out of the study time and 2 were deleted for methodological reasons. The detailed search processes are demonstrated in Figure 1.



**Figure 1.** Follow diagram of systematic review and searches for HBV infection prevalence in I.R. Iran.

### Studies

We found 18 relevant studies (8, 9, 27, 44, 67, 82, 108, 118-120, 171, 191, 202, 209, 216, 247-249) of satisfactory quality in general population. In general population, we excluded another 3 studies because they included subjects with limited age groups which may have confounded the results (44, 118, 209) and one study for low methodological quality (171). So we had 14 studies from 7 (out of 30) provinces in which about 40 percent of the country population live. four studies were from Tehran covering the years from 2001 to 2007 (67, 118, 191, 248), three from Golestan covering 2003, 2004 and 2006 (9, 119, 249), three from East Azerbaijan in 2000 and 2004 to 2005 (8,

108, 202). Other studies were from Hormozgan (2006) (247), Hamadan (2003) (27), Isfahan (2006) (216), and Kermanshah (1999-2003) (82).

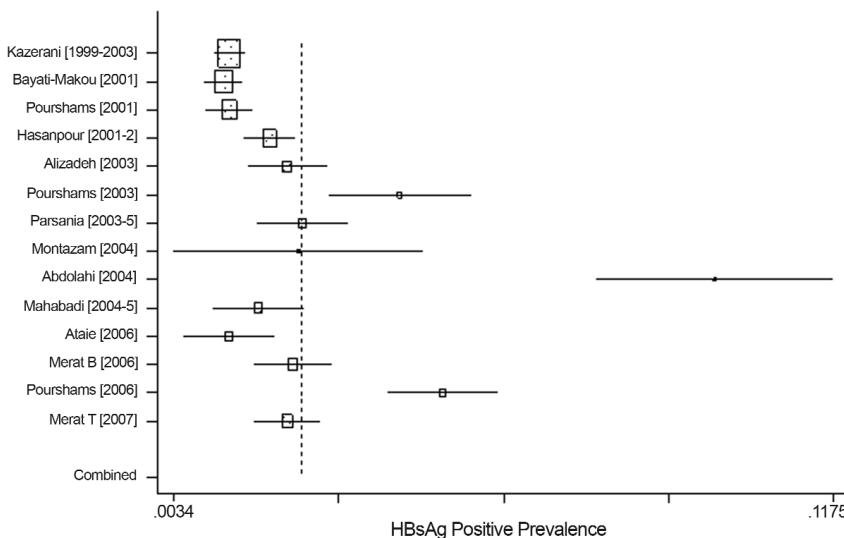
All included studies were cross sectional studies conducted in Iranian population from April 2001 to March 2007 and the sample size range was between 816 and 6820. The age of the study subjects was between 6 and 93 (weighted mean 38.5 years). In the majority of the studies (13 of 15), about 34 to 56 Percent of the study subjects were males while in the other two were 85 and 93 percent. All studies had used ELISA methods that were mainly with Dade Behring, Germany and DiaSorin, Italy ELISA HBsAg detection kits.



**HBV infection prevalence**

The range of the reported HBV prevalence was a wide one from 1.2 percent to 9.7 percent in the general population and the studies showed heterogeneity (Test for heterogeneity:  $Q=161.68$ ,  $df=13$ ,  $p<0.001$ ). According to heterogeneity test, we used random model methods for meta-analysis tests.

The meta-analysis point estimation for HBV prevalence in I.R. Iran between years 2001-2007 was 2.5 percent (95% confidence interval; CI: 2.0-3.1 percent) (Fig. 2).



**Figure 2.** Forest plot of studies about HBV infection prevalence in I.R. Iran.

The distribution of HBV infection prevalence in the country showed that there were significant differences in provinces regarding HBV infection rates and the highest prevalence rate was seen in Golestan (6.3 percent; 95%CI 3.2-9.3 percent).

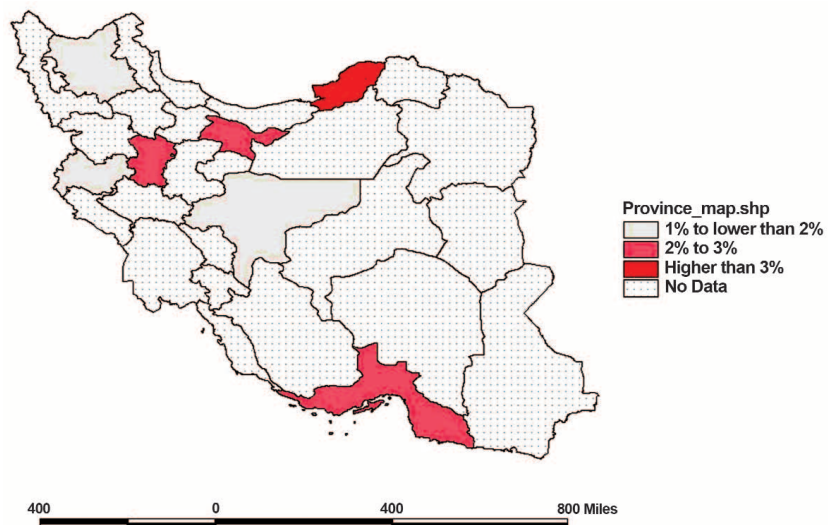
Using survey data analysis method, the HBV infection prevalence in I.R. Iran was estimated at 2.14 percent (95%CI: 1.92-2.35) which seems to be more accurate than meta-analysis method results as explained in the methods section. The HBV infection prevalence in Iranian men and women was estimated at 2.55 percent (95%CI 2.25-2.85) and 2.03 percent (95%CI 1.6-2.46 percent) respectively.

The geographic distribution of HBV infection in Iran showed heterogeneous patterns with the highest prevalence rates (more than 3 percent of the population infected with HBV) in northeastern region

of the country while central and western regions showed the lowest prevalence rates (between 1-2 percent infected) (Fig. 3).

**Discussion**

The HBV infection is a widespread disease that affects large number of populations worldwide and is considered as a major public health problem in many countries. In Iran, the mass vaccination program started in 1993 and reached 94% coverage in 2005 (7). The reported prevalence of HBV infection in Iran decreased from about 3.5% in 1990s (4, 5) to 2.14% in 2000s [current study]. This change is significant but the mass vaccination program is supposed to cause a more significant decrease in HBV infection prevalence. This can be explained by the increasing number of reports on HBV infection in Iran from 28 before 2000s to 236 after 2000. This indicates that the investigations on HBV infection in I.R. Iran have increased significantly about more than 8 times and this may result in less undetermined cases throughout the country and more attention to the infection. This also can result in obviously more accurate prevalence rates. Technology developments also provided more sensitive and accurate diagnostic tools which may explain the slower decreasing trend in HBV infection rates during the past decade despite mass



**Figure 3.** Geographic distribution of HBV infection in I.R. Iran.

vaccination program.

Considering that HBV prevalence reported in Tehran, East Azerbaijan, Isfahan, Hormozgan and Kermanshah in 1999-2000 overlaps with estimates of current study after 2000 we can conclude that the prevalence rate of HBV in these provinces did not change significantly in these years while in new studies the reports showed higher HBV prevalence rates (6).

According to our results, it is estimated that about 1.5 million people in Iran are living with HBV infection and that 15% to 40% of them are at risk of developing cirrhosis and/or hepatocellular carcinoma (HCC) without intervention (1, 251). It is also estimated that 225,000 to 600,000 individuals are at risk of serious health problems related to HBV infection and need immediate attention. Others are HBsAg positive carriers and this large number of carriers may disseminate infection to healthy people vertically or horizontally. Health policy makers should identify and control this large infection reservoir and plan to reduce the transmission rate via improving vaccination program efficiency. Increasing the vaccination coverage rate especially in high risk groups can be an effective plan to control the transmission rate from carriers. These groups are mainly women at their reproductive ages, young people and those with high risk activities or jobs such as health care providers, barbers, drivers and intravenous drug abusers (71, 72, 74). It seems that there is growing evidence about vaccination in adults in Iran supported by changing of transmission routes from vertical and horizontal in childhood to horizontal in adulthood due to some risk factors (252).

Prevalence of HBV infection in males is about 25% higher than females (2.55% vs. 2.03% respectively). This relative but not statistically significant difference can be attributable to exposure to more risk factors such as occupational risk factors in men in Iran.

Heterogeneous pattern of geographic distribution of HBV infection through the country (Fig. 3) indicates that the possible risk factor of HBV infection may differ in different regions of the country and the comprehensive community-based surveys should be conducted to investigate the predisposing factors and risk factors of the infection in these regions to promote the efficiency of interventions and prevention programs.

This study focused on studies between 2001 and 2007 to estimate a more accurate HBV infection prevalence rate that represents an actual prevalence rate at the present time and earlier reports were excluded from analysis.

The systematic reviews in Iran and this study have some limitations especially in using standard search terms in national databases that provide the majority of citations in national prevalence studies. To overcome this problem, we used all synonyms of search terms separately in both Persian and English languages. Another major limitation may be was lack of good coverage in searching universities research projects and student's thesis.

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