

Hepatitis B Vaccination Efficacy in Iranian Healthcare Workers: A Meta-Analysis Study

Milad Azami,¹ Mohammad Reza Hafezi Ahmadi,² and Kourosh Sayehmiri^{3,*}

¹Medical Student, Student Research Committee, Ilam University of Medical Sciences, Ilam, IR Iran

²Associate Professor, Department of Pathology, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, IR Iran

³Associate Professor, Department of Biostatistics, Psychosocial Injuries Research Center, Ilam University of Medical Sciences, Ilam, IR Iran

*Corresponding authors: Kourosh Sayehmiri, Associate Professor, Department of Biostatistics, Psychosocial Injuries Research Center, Ilam University of Medical Sciences, Ilam, IR Iran. E-mail: sayehmiri@razi.tums.ac.ir

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Abstract

Context: Despite various studies, there is no overall estimation about the efficacy of Hepatitis B virus (HBV) vaccine among healthcare workers (including healthcare personnel and healthcare students). The present meta-analysis study was conducted to investigate the efficacy of HBV vaccine in healthcare workers in Iran.

Evidence Acquisition: This study was performed according to the PRISMA guidelines for systematic review and meta-analysis studies. A comprehensive search was conducted using national and international databases including: Magiran, Iranmedex, IranDoc, SID, Medlib, Scopus, Pubmed, Science Direct, Cochrane, Embase, Web of Science, Springer, Wiley online library, Trials Register, DOAJ, and Google Scholar search engine without time limit up to 2016. Just papers which were qualified according to inclusion criteria were examined. The data were analyzed using meta-analysis method in STATA software Ver.11.1.

Results: 1726 healthcare workers had been examined in 12 studies. The efficacy of HBV vaccine, 1-6 months after the injection of the third dose was determined to be 93.1% (95% CI: 90.3 - 97); this rate was 95.9% (95% CI: 93.1 - 98.6) for male and 91.3% (95% CI: 87.1% - 95.5%) for female participants. HBV vaccine efficacy was 90.9% (95% CI: 86.5-95.3) for 8 studies conducted on healthcare personnel and 97.3% (95% CI: 94.7-97.7) for 3 studies on healthcare students.

Conclusions: Immunogenicity of HBV vaccine was 90 - 97 in healthcare workers. Hence, the complete course of vaccination is sufficient for prevention of HBV and there is no need for booster dose or dose re-administration.

Keywords: Hepatitis B, Vaccine Efficacy, Clinical Students, Healthcare Workers, Meta-Analysis

1. Context

Hepatitis B virus (HBV) infection is a major infectious disease with worldwide prevalence (1, 2). 1 - 2 billion people are estimated to be afflicted with HBV (2, 3), and 0.4% of healthcare workers (HCW) are suffering from the disease (4). In addition to reducing the level of exposure and taking protective measures during diagnostic and therapeutic procedures, vaccination currently is the most effective way to prevent HCWs from HBV (5, 6). Iran has been conducting the vaccination program for high-risk groups, such as medical staff and clinical students, at intervals of 0, 1, and 6 months since 1993 (7). Systematic reviews and meta-analysis studies have reported the rate of HBV vaccination coverage to be 70.1%, 73%, and 72.2% for physicians, nurses, and dentists in Iran, respectively (8-10). Since the contact with infected blood is a possible route of disease transmission, HCW is at high risk of HBV (11). Anti-HBs titer is used to evaluate the efficacy of HBV vaccine and the levels of anti-HBs higher than 10 mIU/mL are considered as a positive response (12). Several studies conducted to evaluate the efficacy of HBV vaccine among HCWs in Iran have

estimated the efficacy of the vaccine to be 67% - 100% (13-29). The most important factors affecting the efficacy of HBV vaccine include: age, gender, genetics, smoking, vaccine type, vaccination dose, injection site, and the period after the last injection of vaccine (30-34).

2. Objectives

Meta-analysis is a process, in which data of various researches, which share common ground, are collected and analyzed to get an authentic estimation of the effects of some medical interventions (35). It is quite clear that, considering the amalgamation of the data of several separate researches, meta-analysis methods occupy larger sample sizes, less chances and possibilities, and increased significance of statistical findings. Specific conditions necessary for the implementation of meta-analysis make it a very reliable procedure. Given the mixed results of HBV vaccine efficacy among HCWs, we intend to examine all related reports and finally present a rough estimate of the general condition through a meta-analysis study (36, 37).

3. Data Sources

The present study was performed according to the PRISMA guidelines for systematic review and meta-analysis studies (37). To avoid bias, two researchers independently performed all steps of meta-analysis including database searching, study selection, quality assessment, and data extraction. A comprehensive search was conducted based on national and international databases: Magiran, Iranmedex, IranDoc, SID, Medlib, Scopus, Pubmed, Science Direct, Cochrane, Embase, Web of Science, Springer, Wiley online library, Trials Register, DOAJ, and Google Scholar search engine without time limit up to 2016. Persian and English keywords compatible with MeSH terminology were used; these keywords included "Hepatitis B", "Antibody", "Vaccination", "Vaccine", "Immunization", "Immunogenicity", "Efficacy", "Healthcare", "Health Personnel", "Students", "Iran" and combined words using AND/OR Boolean operator. The combined search for PubMed is shown in Appendix 1.

3.1. Definitions

HBV vaccination response was considered positive when the antibody level was more than 10 (Anti-HBS > 10 mIU/mL). Healthcare workers included both healthcare students such as any students under education in hospitals and healthcare personnel such as any staff employed in hospitals, health centers affiliated in Iran in this study. (12).

3.2. Inclusion and Exclusion Criteria

Inclusion criteria included all HCWs with a history of HBV vaccination, and the time interval of 1-6 months since the last vaccination.

Exclusion criteria were lack of full vaccination at the time intervals of 0, 1, and 6 months, smoking, taking immunosuppressive drugs, uncertainty in regard to the time of the last vaccination, Anti-HBC (+) and HBs Ag (+), cases with booster dose of HBV vaccine, irrelevant studies, and insufficient data.

3.3. Quality Assessment

The researchers examined the quality of the selected studies in the next step using STROBE (38) as a standard checklist. This checklist included 22 items covering all aspects of the methodology of studies, such as sampling techniques, measured parameters, statistical analyses, and objectives. Each item was scored from 0 to 2 in the checklist and maximum possible score was 44. Consequently, the studies were divided into three categories: low quality with a score below 15.5, moderate quality with a score of

15.5 - 29.5, and high quality with a score of 30 - 40; those studies which gained the minimum score (15.5) were selected for the meta-analysis study.

4. Data Extraction

All papers which finally entered the process of this study were extracted according to a pre-prepared checklist. The checklist collected the following information: author's name, year of study, place of study, type of study, sample size, medical personnel sample size, clinical students sample size, age and vaccine efficacy, for male and female separately.

4.1. Statistical Analysis

Variance of each study was calculated according to binomial distribution. Cochran test and I^2 index were used to assess the heterogeneity of the studies. The heterogeneity in the present study was 88.8% indicating a high heterogeneity (I^2 index less than 25% means low heterogeneity, 25% to 75% moderate heterogeneity, and more than 75% high heterogeneity) (39, 40). Regarding the significant heterogeneity index (I^2), random effects model was used to pooled analysis in this meta-analysis. The studies were mixed together based on variance and sample size. Meta-regression model was used to find the relationships between vaccine efficacy and the year and sample size of the study. Subgroup analysis was done according to region and risk groups. STATA software Ver.11.1 was used to analyze the data. Egger test was performed to check publication bias. Egger test can indicate a symmetrical or asymmetrical funnel plot. $P < 0.05$ was considered as the significance level of the study.

5. Results

220 papers, after removing another 160 due to being repetitive, were identified in the systematic review. After analyzing the full text of 82 papers, 70 papers were eliminated for not meeting the inclusion criteria. Finally, 12 papers comprising 1726 healthcare workers (1388 healthcare personnel and 338 healthcare students) published during 1998-2015 were qualified to enter the meta-analysis study. Mean age of medical staff was 31.98 (confidence interval of 95%: 28.25 - 38.69) while the age range of clinical students was 20 - 26 years (Figure 1).

The efficacy of HBV vaccine, 1 - 6 months after the last dose of hepatitis B vaccination was estimated to be 93.1% (95% CI [Confidence Interval]: 90.3% - 97%) among HCWs. The lowest (76.4%) and highest (100%) rates were related to studies in Babol (2003) and Isfahan (1998), respectively.

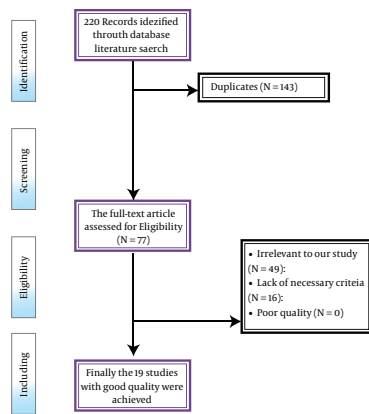


Figure 1. The Entrance Flowchart of Systematic Review and Meta-Analysis

The efficacy of HBV vaccine based on geographical region is presented in [Figure 2](#), which shows that the western part of Iran the most positive response as 97% ([Tables 1 - 3](#)).

HBV vaccine efficacy was 90.9% (95% CI: 86.5 - 95.3) for 8 studies conducted on medical staff and 97.3% (95% CI: 94.7 - 97.7) for 3 studies on clinical students.

In regard to the immune response of HBV vaccine in health care staff and medical personnel, the rate was 95.9% (95% CI: 93.1 - 98.6) in males and 91.3% (95% CI: 87.1 - 95.5) in females ([Figures 3 and 4](#)).

[Table 4](#) shows the efficacy of HBV vaccine separately in clinical students and medical staff based on gender; the highest rate (99.6%) was related to male clinical students.

Meta-regression model was used to investigate the possible causes of heterogeneity of studies; P value was 0.964 for the year of study and 0.314 for sample size, indicating that was no statistically significant. According to [Figure 5](#), publication bias had a significant effect on the results of these studies by showing a symmetrical funnel plot. The size of circles indicates the weight of the study; larger circles indicates larger sample sizes.

6. Discussion

The present study is the first systematic review and meta-analysis conducted to evaluate the efficacy of HBV vaccine during 1 - 6 months after the injection of the last dose of HBV vaccine among high-risk group including medical students and medical staff. The efficacy of HBV vaccine was sub-grouped by geographical region, gender, year of the study, and sample size. Iran initiated the vaccination program in 1993, and according to the studies, this program covers more than 70% of health care system personnel two decades after the implementation ([8-10](#)).

The exclusion criteria were smokers, taking immunosuppressed drugs, positive HBC antibody, positive HBs-Ag, booster dose injection, lack of full injection at 0, 1, and 6-month intervals, and non-Iranian samples. After examining 1726 HCWs in 12 studies, the efficacy of HBV vaccine, 1- 6 months after the last dose administration was estimated as 93.1%; reports from other countries in this regard are shown in [Table 5 \(41-46\)](#).

The type of vaccine used in the present study was recombinant which, compared to plasma-derived vaccine, had higher efficacy in the same period, although the difference between two vaccines was not significant. According to the study of [Chen et al. \(47\)](#), the efficacy of both recombinants and plasma-derived vaccines was similar in creating anti-HBs Ab. HBV vaccine injection mode in studies met to this meta-analysis, was intramuscular. In [Chen's](#) systematic study, intramuscular injection at a dose of 20 mg was significantly more effective than intradermal injection at a dose of 2 mg ([47](#)).

To indicate the effect of age on HBV vaccine efficacy, sub-group analysis was conducted based on two risk groups of clinical students (aged 20 - 26 years) and medical staff (mean age of 31.98 years). The results showed that the efficacy of the vaccine was higher in clinical students and, since their confidence intervals did not intersect, this between-group difference was statistically significant. Study of [Rezaee et al.](#), conducted on Iranian children, revealed that there is no significant relationship between age and immune response ([48](#)). Other studies, such as those carried out by [Chathuranga et al.](#) in Sri Lanka ([44](#)) and [Yen et al.](#) in China ([45](#)), did not find any significant relationship between age and immune response, too. According to the present study, the efficacy of HBV vaccine was higher in male than female HCW, this difference was not statistically significant. Other studies have presented contradictory reports on the relationship between gender and HBV vaccine efficacy. For example, [Thakur](#) in India and [Chathuranga et al.](#) in Sri Lanka stated that HBV vaccine immune response was much higher in women than men ([42-44](#)). [Thomas's](#) study did not recognize the gender of participants as an effective factor in immune response; a finding that is consistent with that of [Holenger's](#) research indicating the weak role of gender in HBV vaccine immunogenicity ([49](#)).

In the current meta-analysis, publication bias had a significant effect on the results of the studies. Since papers providing positive results have higher chances of publication, studies that focus on relationship assessments are usually influenced by bias. However, the present study which examined the efficacy of HBV vaccine is free of such bias.

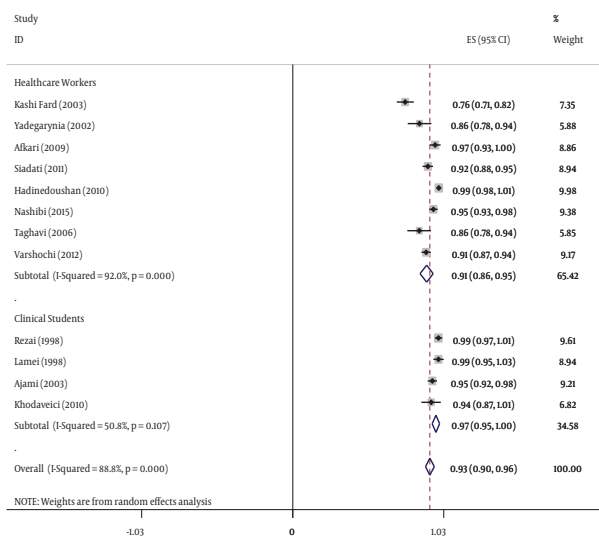


Figure 2. Forest Plot of the Hepatitis B Vaccine Efficacy Separately Healthcare Students and Healthcare Personnel According to Anti-HBS Criteria Obtained by Random-Effects Model; the Midpoint of Each Line Segment Shows the Percentage Values; the Length of Line segments Shows 95% Confidence Interval in Each Study; Diamond Mark Shows the Efficacy of the Vaccine for all Studies

Table 1. Details of Studies Entered the Meta-Analysis

Author Name	Location	Year	Sample Size	Risk Group	Average Age, y	Time Elapsed Since the Last Doses, mo	Vaccine	Doses of Vaccine, μ g	The Injection Method	Vaccine Efficacy (%) AntiHBS > 10 mIU/ml.
Kashifard	Babol	2003	240	medical staff	37	3	HeperBiovax	20	intramuscular	76.4
Yadegarinia	Tehran	2002	72	medical staff		3	Heber Biovac	20	intramuscular	86.1
Alkari	Lar	2009	90	medical staff	38.5	3-4			intramuscular	96.7
siyadat	Babol	2011	230	medical staff	30	3	Recombinant		intramuscular	91.7
HadiNadooshan	Yazd	2010	126	medical staff	22.4	4	Recombinant	100	intramuscular	99.2
Rezaei	Esfahan	1999	65	Student		1-2	Recombinant	20	intramuscular	100
lamei	Urmia	1998	30	Student	34	1				100
Ajami	Sari	2003	193	Student	20-24	1-2	Recombinant			94.8
Nashibi	Ahvaz	2015	239	medical staff		1-6				95.6
Khodaveisi	Hamadan	2010	50	Student	19-29	4	Recombinant		intramuscular	94
Taghavi	Tehran	2006	72	medical staff		1	Recombinant	20	intramuscular	85.9
Varshuchi	Tabriz	2012	319	medical staff	32	3	EUVAXB			90.6

Table 2. Estimated Efficacy of Hepatitis B Vaccine Sub-grouped by Risk Group

Risk Group	The Number of Studies	Sample Size	I ²	Confidence Interval (95%)	Total Estimated, %
Healthcare personnel	8	1317	92	86.5 - 95	90.9
Healthcare students	4	338	80.8	95 - 97.7	97.2

Table 3. Estimates of Hepatitis B Vaccine Efficacy Sub-grouped by Gender

Gender	The Number of Studies	Sample Size	I ²	Confidence Interval (95%)	Total Estimated, %
Male	8	380	86.7	93.1 - 98.6	95.9
Female	8	904	84.2	87.1 - 95.5	91.3

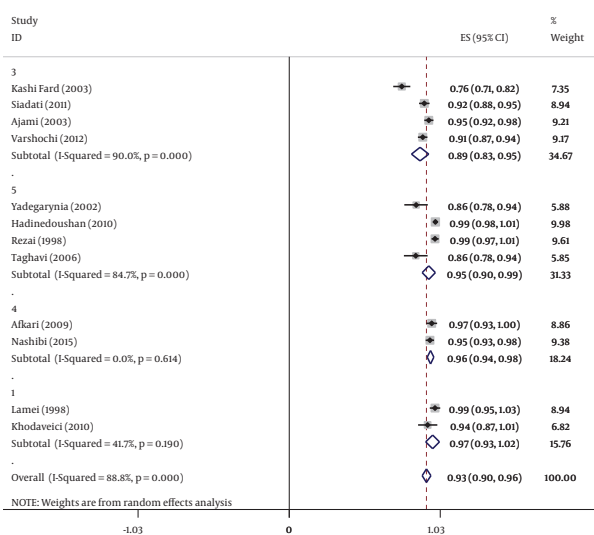


Figure 3. Forest Plot of the Hepatitis B Vaccine Efficacy in Iranian Healthcare workers Separately in Different Geographical Areas According to Anti-HBS Criteria Obtained by Random-Effects Model; the Midpoint of Each Line Segment Shows the Percentage Values; the Length of Line Segments Shows 95% Confidence Interval in Each Study; Diamond Mark Shows the Efficacy of the Vaccine for all Studies (1 = West, 2 = East, 3 = North, 4 = South 5 = Center).

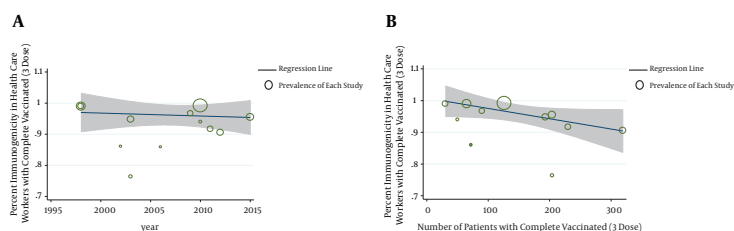


Figure 4. Meta-Regression Plots for the Efficacy of Hepatitis B Vaccination According to Year of Study and Sample Size

Table 4. Estimates of Hepatitis B Vaccine Efficacy Separately in Clinical Students and Medical Staff Based on Gender

Genus	Group	The Number of Studies	Sample Size	I2	Confidence Interval	Total Estimated, %
Male	Medical Staff	6	341	90.3	90.3 - 97.7	94
	Clinical students	2	39	0	97.8 - 100	99.6
Female	Medical Staff	6	700	88.7	84.8 - 96.2	90.5
	Clinical students	2	204	0	90.3 - 97	93.7

6.1. Weak and Strong Points of the Study

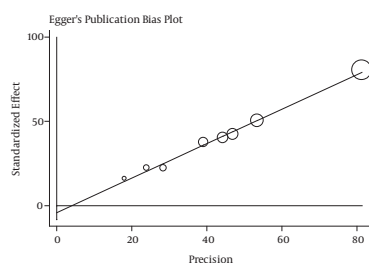
Disregarding efficacy of HBV vaccine based on smoking, booster dose administration, and irregular vaccination is the most important weak point of the present study; therefore, it is recommended that further meta-analysis studies investigate the effect of such factors on vaccine immune response.

On the other hand, the strong points of the study included: 1) precise estimation of HBV vaccine efficacy

Table 5. hepatitis B Vaccine Efficacy Reported in Some Overseas Studies

Author(s)	Country	Sample Size	Group	Age, y	Type of Vaccine	Time Elapsed Since the Last Doses	Vaccine Efficacy, %
Thakur et al. (41)	Northern India	381	HCW	18 - 45	Recombinant hepatitis B	1 mo	96.4
Beran et al. (42)	Czech Republic	209	General Population	26 - 30	Twinrix™, GSK Vaccines, Belgium	15 y	81.8
Thomas et al. (43)	India	454	HCW	16 - 50	Recombinant hepatitis B	1 y	98.1
Chathuranga et al. (44)	Sri Lanka	99	HCW	-	-	1 - 7 y	86.6
Yen et al. (45)	Taiwan	250	HCW	25 - 70	Recombinant hepatitis B	8 mo	86.4
Wang et al. (46)	China	348	Healthy young adults	18 - 25	Recombinant hepatitis B	1 mo	97.7

Abbreviation: HCW, health care workers.

**Figure 5.** Funnel Plot for Checking Publication Bias (P-Value = 0.45)

among originally Iranian health care staff and medical students through applying criteria which can affect immunogenicity; 2) evaluating HBV vaccine efficacy sub-grouped by medical students and medical staff to show the relationship between age and HBV vaccine efficacy.

6.2. Limitations of the Study

1) There were not sufficient internal sources for searching keywords.

2) The time passed since the administration of the last dose was not mentioned in some studies, while some others did not present an accurate description of the mentioned time.

3) Some studies had investigated the effect of vaccine on immune system among all vaccinated subjects (both incomplete and complete courses of vaccination) and this caused the removal of such studies from the meta-analysis.

6.3. Conclusions

Efficacy of HBV vaccine was 90 to 97% in HCWs. Hence, the complete course of vaccination is sufficient for HBV and there is no need for booster dose or dose re-administration.

Supplementary Material

Supplementary material(s) is available [here](#).

Acknowledgments

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Footnotes

Authors' Contribution: All authors: data collection; Kouros Sayehmiri: statistical analysis; Milad Azami: study design; Kouros Sayehmiri, Milad Azami: quality assessment; all authors: final revision and grammar editing.

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Conflict of Interests: No conflict of interest is reported by the authors of the present study.

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