



Efficacy of Hepatitis B Vaccination in Under Five-Year-Old Children in Iran: A Systematic Review and Meta-Analysis Study

Fatemeh Najafi,¹ Kourosch Sayehmiri,^{2,*} and Reza Najafi³

¹PhD Student of Nursing, Department of Internal- Surgical Nursing, School of Nursing and Midwifery, Tehran University of Medical Sciences, Tehran, Iran

²Health Faculty, Biostatistics Department, Ilam University of Medical Sciences, Ilam, Iran

³Pediatric Endocrinology Department, Ilam University of Medical Sciences, Ilam, Iran

*Corresponding author: Professor Kourosch Sayehmiri, Health Faculty, Biostatistics Department, Ilam University of Medical Sciences, Ilam, Iran. Tel: +98-9183410782, E-mail: sayehmiri@razi.tums.ac.ir

Received 2017 December 21; Revised 2018 April 22; Accepted 2018 April 23.

Abstract

Context: Hepatitis B viral infection, specially in children, is an unsolved global health issue. National and international vaccination programs, as the main means to prevent this infection, have been operating for years. This meta-analysis study was launched to investigate the vaccination efficacy in under five-year-old children in Iran.

Evidence Acquisition: In this research, all national databases including, SID, Magiran, Iran medex, Iran doc, and Medlib, as well as international databases, including PubMed, Medline, and ISI were searched for published articles associated with evaluation of seroconversion rates after hepatitis-B vaccination in Iranian children. The search was performed in the Persian and/or English language and in under five-year-old children in Iran. The variance of each study was calculated using the binomial distribution formula. The results of studies were combined using random-effects meta-analysis model. Data were analyzed using STATA version 12.

Results: In the present research, 11 studies, performed from 2000 to 2017, were investigated. The number of samples in these 11 studies were 3063 children (1592 males and 1471 females). In the studies, the efficacy range of the hepatitis-B vaccine in under five-year-old children in Iran was 89% (95% CI: 86% - 93%) with high heterogeneity (P value for heterogeneity was 0.001, $I^2 = 92.9$). Range of efficacy for males and females was 85% (95% CI: 78 to 91) and 88% (95% CI: 83 to 93), respectively.

Conclusions: The hepatitis B virus (HBV) vaccination program in Iran seems to be highly effective although some questions, such as the effect of gender on responsiveness to vaccine and heterogeneity of different data, remain unclear.

Keywords: Hepatitis-B, Efficacy, Meta-Analysis, Vaccine, Iran

1. Context

Currently, hepatitis B remains a health problem all over the world, as it can potentially affect more than 2 billion people worldwide (1). Hepatitis B infection, especially in cases with the chronic form, is associated with severe conditions, such as cirrhosis and hepatocellular carcinoma (HCC) (2). The most susceptible groups to develop the chronic form of hepatitis B are infants and children under five years old (3). As hepatitis B virus persists in body fluids, the main transmission routes are mother to newborn transmission, sexual intercourse, IV drug administration, and occupational contact (4). According to the latest meta-analysis of HBV infection, prevalence in Iran varies from 0.87% to 8.86% in different provinces (5). About 5% of infected individuals will remain as chronic carriers and thus vaccination against HBV is an efficient way to stop spreading of infection (6). In order to prevent HBV infec-

tion in 1991, the world health organization (WHO) asked its members to start a national vaccination program, especially in endemic regions (7). In Iran, an infant vaccination program was started in 1993 and it is claimed that over 98% of infants are covered (8). Vaccination in children could prevent both acute and chronic forms of infection and reduce complications of HBV infection. Vaccination with HBV subunit vaccine is correlated with a protective level of humoral immunity in 90% of vaccinated cases, yet the titer of antibody could decline over time (9). Anti-HBs antibody titration is considered as a means to evaluate protection in vaccinated individuals. Cases with more than 10 mIU/mL of anti-HBs antibody are assumed as protected (10). The persistence of immunity against HBV in vaccinated individuals depends on immunological memory and high antibody titer (11). Despite high efficacy of vaccination against HBV in Iran (67% to 100% efficacy), some factors such as age,

gender, vaccination dosage etc., seem to affect the vaccination efficacy (12). Also it has been documented that some cases constitutively show no response to HBV vaccination (13). Specially in children, a lack of response to HBV vaccine has been shown, which may be due to immune deficiencies, genetic disorders or improper vaccination procedures (14). According to other meta-analysis studies in Iran, the efficacy of hepatitis vaccination varies in different ethnic groups and different subjected sub-populations. A recent meta-analysis study reported 86.3% vaccination efficacy in the general population yet 59.6% in specific patient subpopulations (15). Another meta-analysis showed 93.1% protection among health staff, six month after vaccination (12). Although several meta-analysis studies have investigated HBV vaccination program efficacy in different populations in Iran, yet none of them exclusively surveyed HBV vaccination efficacy in under five-year-old children (8, 12, 15). Regarding the mentioned data about the importance of protective immune response against HBV in infants and young children and considering the possibility of lower immune response in this population, this study performed a systematic review and meta-analysis to investigate HBV vaccination protectivity and efficiency in children under five years age in Iran and summarized the present data on this issue.

2. Objective

A systematic review and meta-analysis was carried out using published articles associated with evaluation of seroconversion rates after hepatitis-B vaccination efficacy in under five-year-old children in Iran.

3. Data Sources

All databases including SID, Magiran, Iranmedex Iran-doc, Medlib, PubMed, Medline, and ISI from 2000 to 2017, were searched using keywords and all possible combinations: Hepatitis B, vaccination, efficacy, children, and Iran. Also, titles from the search and references in the selected articles were used as additional search tools.

4. Study Selection

The selection of articles for the study was based on three stages, title, abstract, and full text. Studies with inadequate information, review studies, congresses abstracts, studies published in languages other than English and Persian, systematic studies, meta-analysis, and repeated studies were excluded from the analysis.

The main criterion for Inclusion of different articles in this research was Reference to the efficacy of the hepatitis-B vaccine in under five-year-old children in Iran.

The exclusion criteria of studies included no mention of efficacy of hepatitis-B vaccine, sample with age of over five years old, review studies, and repeated studies. The researchers initially collected all articles related to the efficacy of hepatitis-B vaccine in Iranian children. Then, a checklist of abstracts was prepared. In this phase, 142 articles, which mentioned in their title "The efficacy of hepatitis B vaccine in Iran", were included in the initial list. Subsequently, each single article was independently studied, 22 of them were removed due to duplication, 42 articles were excluded as their subjects were over five years old, 14 articles due to the inaccessibility of full text, and 17 meta-analysis and review articles were also removed (Figure 1).

5. Data Extraction

After selecting high-quality articles, 11 publications were examined by two reviewers, independently, using a checklist of information that was designed for data extraction.

Finally, for the selected articles, the following data, first author, year of publication, place of study, sample size, age, gender, type of vaccine and percentage of efficacy of hepatitis-B vaccine, was extracted (Table 1).

Statistical analyses for particular factors were performed using the STATA software version 11.2 (STATA Corp LP, College Station, TX, USA) for Windows. The variance of each study was calculated using the binomial distribution formula. Statistical heterogeneity between studies was assessed using Moran's I^2 and Cochran's Q-tests (at alpha/significance level < 10%). Meta-regression was used to estimate the efficacy of hepatitis-B vaccine efficacy in under five-year-old children in Iran. The results of studies were combined using the random-effects meta-analysis model. A P value of less than 0.05 for heterogeneity tests was considered significant.

6. Results

In the present study, 11 publications (11 studies) were included in the review. Figure 2 shows a flowchart of the search strategy and study selection, along with the reasons for exclusions. In total, 3063 children (1592 males and 1471 females) were examined in these studies.

The results showed that hepatitis-B vaccine efficacy in under five-year-old children in Iran was 89% (95% CI: 86% to 93%) with high heterogeneity (P value for heterogeneity, < 0.001, $I^2 = 92.9$).

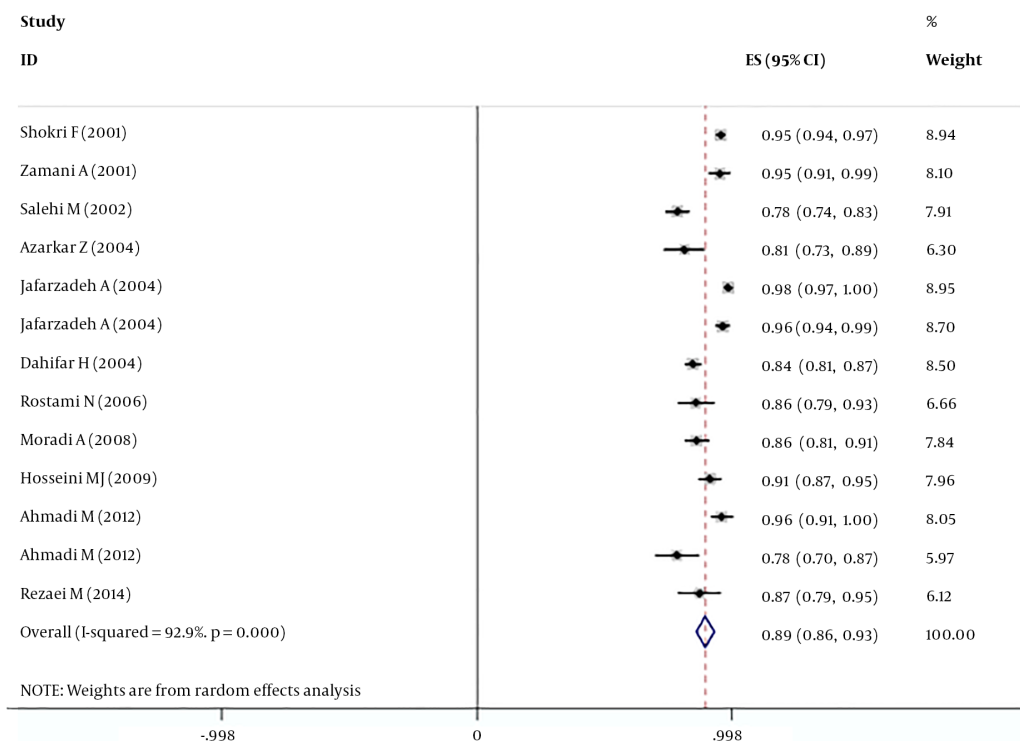


Figure 1. The Efficacy of the hepatitis-B vaccine in under five-year-old children in Iran based on random effects model Midpoint of each segment is the estimate of prevalence and segment lengths show the 95% CI for each study. The diamond mark shows the prevalence in the country for all studies.

Table 1. The Characteristics of Different Articles Related to the Efficacy of Hepatitis-B Vaccine Efficacy in Under Five-Year-Old Children in Iran

Authors Name	Years	Location	Sample Size	Age	Type of Vaccine	Dose of Vaccine, μ g	Vaccine Efficacy AntiHBS > 10, mIU/mL, %	Mean of HBsAb, mIU/mL
Moradi A (14)	2008	Gorgan	215	7 - 12, mo	Euvax B, aKorean		86	173.5
Ahmadi M (16)	2012	Bandarabbas	92	12 - 15, mo	NA		95.66	231
Ahmadi M (16)	2012	Bandarabbas	94	21 - 24, mo	NA		78.2	142.9
Azarkar Z (6)	2004	Mashad	100	12 - 16, mo	Eberbiovac		81	
Salehi M (17)	2002	Zahedan	324	15 - 23, mo	Herberbiovac		78.4	
Shokri F (18)	2001	Kerman	735	Neonate	Herberbiovac	10	95.2	302
Rostami N (19)	2006	Orumie	97	15, mo	Heberbiovac	10	85.6	
Rezaei M (20)	2014	Semnan	67	< 5, y	Cuban Vaccine		87	
Hosseini MJ (21)	2009	Tehran	165	1.5 - 5	NA		91	232.64
Jafarzadeh A (22)	2004	Urmia	290	Neonate	Herberbiovac	10	98.3	
Jafarzadeh A (22)	2004	Kerman	231	Neonate	Herberbiovac	10	96.1	
Zamani A (23)	2001	Tehran	115	12 - 24, mo	Heber Biotec	10	94.8	
Dahifar H (24)	2004	Tehran	538	15 - 45, mo	Herberbiovac	10	84.4	294
Total			3063					

The highest and lowest hepatitis-B vaccine efficacy was observed in the study of Jafarzadeh et al. in Uromie (north-west of Iran) and Ahmadi et al. in Bandarabbas (south of

Iran) in that efficacy was 98.3% (95% CI: 97 to 100) and 78.2% (95% CI: 70 to 87), respectively (Table 1).

The efficacy of the hepatitis-B vaccine in males and fe-

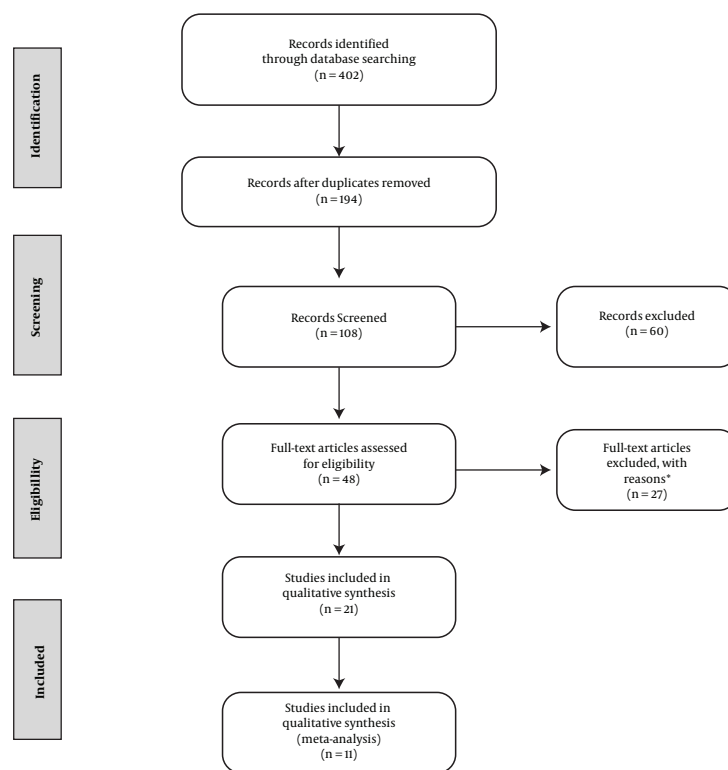


Figure 2. Prisma flow diagram illustrating selection of articles

males was 85% (95% CI: 78 to 91) and 88% (95% CI: 83 to 93), respectively.

General information about selected papers in this study is listed in Table 1. Figure 1 shows the efficacy of the hepatitis-B vaccine in under five-year-old children in Iran, based on the random effects model.

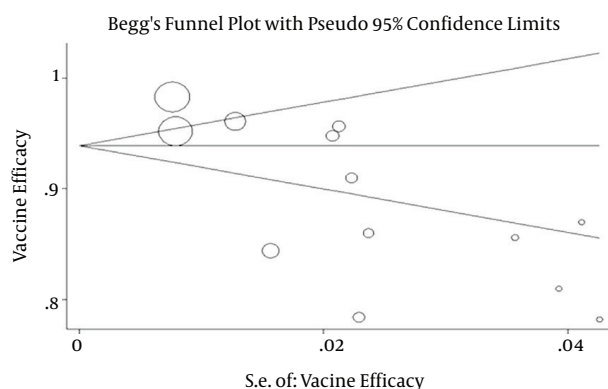


Figure 3. Begg's funnel plot for publication bias

7. Conclusions

Despite national and international vaccination programs, HBV infection is still a global health concern with certain morbidity (25). One of the most susceptible populations to be effected by HBV and to develop chronic form of HBV infection is under five-year-old children (26). The current meta-analysis is the first to study the efficacy of HBV vaccination, specifically in the under five-year-old population. This study investigated published data on HBV vaccination efficacy in children under five years old in Iran from 2001 to 2014. The results showed heterogeneity in vaccine efficacy among different studies and the efficacy of hepatitis-B vaccine in under five-year-old children in different studies from Iran was 89% (95% CI: 86% - 93%). Also, the efficacy of HBV vaccination in females was somewhat more than males. Other meta-analysis studies on general populations also showed different efficacies of HBV vaccination in different provinces of Iran (8, 12, 15). This indicates the importance of launching a national study to survey HBV vaccination efficacy in different ethnic groups. According to different studies, the effect of age groups and gender on responsiveness to HBV vaccine has been controversial and still remains unclear and needs to be investigated further.

The study of Tazhibi et al. showed that efficacy in adults was higher than children (15). Also Azami et al., in contrary to the results of the present study, showed that the efficacy of HBV vaccination in males was higher than females (12). Yen et al. in China did not report any relationship between age and responsiveness (27). Overall, the vaccination program was shown to be highly effective in the studied population. In other countries, similar results have been reported. For example, a study in Colombia showed 75% HBV infection reduction in children of highly endemic areas (28). In China, where the vaccination program has started from 1992, the efficacy of HBV vaccination in the general population was estimated as 88.3% (29). One reason to explain the higher responsiveness of HBV vaccination in the current study compared to others could be age of subjected population since studies showed that as vaccinated individuals grow the titer of HBV antibodies declines and older vaccinated cases need booster shots to remain protected (30). Similar to other studies, the current study had its own limitations, such as lack of access to other data resources except online data and lack of access to detailed data like hygiene conditions of subjected cases and other risk factors. Also, sources of vaccines and the antibody titration methods may be effective factors, which were not included here.

7.1. Conclusion

Generally, this meta-analysis study showed that despite a high efficacy of HBV vaccination in Iran among under five-year-old children, due to heterogenic data from different provinces, a study with national coverage is required to investigate the effective factors on vaccination efficacy.

References

- Trepo C, Chan HL, Lok A. Hepatitis B virus infection. *Lancet*. 2014;**384**(9959):2053-63. doi: [10.1016/S0140-6736\(14\)60220-8](https://doi.org/10.1016/S0140-6736(14)60220-8). [PubMed: [24954675](https://pubmed.ncbi.nlm.nih.gov/24954675/)].
- Ding X, Yang Y, Han B, Du C, Xu N, Huang H, et al. Transcriptomic characterization of hepatocellular carcinoma with CTNNB1 mutation. *PLoS One*. 2014;**9**(5). e95307. doi: [10.1371/journal.pone.0095307](https://doi.org/10.1371/journal.pone.0095307). [PubMed: [24798046](https://pubmed.ncbi.nlm.nih.gov/24798046/)]. [PubMed Central: [PMC4010419](https://pubmed.ncbi.nlm.nih.gov/PMC4010419/)].
- Rukunuzzaman M, Karim MB. Chronic Hepatitis B in Children - A Review. *Mymensingh Med J*. 2015;**24**(3):649-56. [PubMed: [26329971](https://pubmed.ncbi.nlm.nih.gov/26329971/)].
- Daniels D, Grytdal S, Wasley A, Centers for Disease C.Prevention. Surveillance for acute viral hepatitis - United States, 2007. *MMWR Surveill Summ*. 2009;**58**(3):1-27. [PubMed: [19478727](https://pubmed.ncbi.nlm.nih.gov/19478727/)].
- Mohammadi Z, Keshkar 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](https://doi.org/10.15171/mejdd.2016.01). [PubMed: [26933476](https://pubmed.ncbi.nlm.nih.gov/26933476/)]. [PubMed Central: [PMC4773083](https://pubmed.ncbi.nlm.nih.gov/PMC4773083/)].
- Azarkar Z. [Efficacy of hepatitis-B vaccine in children from 12 to 16 months in Mashad health centers]. *J Qazvin Univ of Med Sci*. 2004;**(29)**:38-41. Persian.
- World Health Organization. *Expanded programme on immunisation Report of 14th Global Advisory Group*. Geneva: WHO; 1991.
- Rezaee R, Aghcheli B, Poortahmasebi V, Qorbani M, Alavian SM, Jazayeri SM. Prevalence of National Responsiveness to HBV Vaccine After 22 Years of Iranian Expanded Program on Immunization (EPI): A Systematic Review and Meta-Analysis Study. *Hepat Mon*. 2015;**15**(5). e23618. doi: [10.5812/hepatmon.15\(04\)2015.23618](https://doi.org/10.5812/hepatmon.15(04)2015.23618). [PubMed: [26045701](https://pubmed.ncbi.nlm.nih.gov/26045701/)]. [PubMed Central: [PMC4451270](https://pubmed.ncbi.nlm.nih.gov/PMC4451270/)].
- Rafizadeh B, Kazemi AN, Amir Moghaddami HR, Mousavinasab M. [Survey of Anti-HBs Serum level in vaccinated 7-9 year-old children in Zanjan City 2004]. *Zanjan Univ Med Sci*. 2004;**12**(47):49-55. Persian.
- Fisman DN, Agrawal D, Leder K. The effect of age on immunologic response to recombinant hepatitis B vaccine: a meta-analysis. *Clin Infect Dis*. 2002;**35**(11):1368-75. doi: [10.1086/344271](https://doi.org/10.1086/344271). [PubMed: [12439800](https://pubmed.ncbi.nlm.nih.gov/12439800/)].
- Jafarzadeh A, Rashidi-Nejad H, Hassanshahi G, Montazerifar J, Mozafari A, Nejad-Ghaderi M. [Evaluation of Serum Anti-Hbs Concentration in Children Vaccinated with Recombinant Hepatitis B Vaccine at Birth]. *J Shahid Sadoughi Univ Med Sci*. 2006;**14**(2):23-8. Persian.
- Azami M, Hafezi Ahmadi MR, Sayehmiri K. Hepatitis B vaccination efficacy in Iranian healthcare workers: A meta-analysis study. *Hepat Mon*. 2016;**17**(1). doi: [10.5812/hepatmon.37781](https://doi.org/10.5812/hepatmon.37781).
- Schonberger K, Riedel C, Ruckinger S, Mansmann U, Jilg W, Kries RV. Determinants of Long-term protection after hepatitis B vaccination in infancy: a meta-analysis. *Pediatr Infect Dis J*. 2013;**32**(4):307-13. doi: [10.1097/INF.0b013e31827bd1b0](https://doi.org/10.1097/INF.0b013e31827bd1b0). [PubMed: [23249904](https://pubmed.ncbi.nlm.nih.gov/23249904/)].
- Moradi AAV, Khoda Bakhsi B, Ghaemi EA, Mansourian AR, Sari Khani AA, Saeidi M. [The response rate to hepatitis B vaccination in children younger than one year of Gorgan]. *J Gorgan Univ Med Sci*. 2008;**10**(2):50-3. Persian.
- Tazhibi M, Hajivandi A, Tafti AD, Fallahzadeh H. The efficacy of hepatitis B vaccine in Iranian population: A systematic review and meta-analysis. *J Educ Health Promot*. 2014;**3**:53. doi: [10.4103/2277-9531.134741](https://doi.org/10.4103/2277-9531.134741). [PubMed: [25077146](https://pubmed.ncbi.nlm.nih.gov/25077146/)]. [PubMed Central: [PMC4114169](https://pubmed.ncbi.nlm.nih.gov/PMC4114169/)].
- Ahmadi M, Moosavi SM, Jahansfar F. [Comparison of antibody level in post hepatitis B vaccination in children with 12-15 and 21-24 months age]. *J Gorgan Univ Med Sci*. 2012;**4**(2):59-65. Persian.
- Salehi M, Saneimoghadam E, Khosravi S. Evaluation of immune response of hepatitis B vaccination in Zahedan infants. *Zahedan J Res Med Sci*. 2002;**4**:155-8.
- Shokri F, Jafarzadeh A. High seroprotection rate induced by low doses of a recombinant hepatitis B vaccine in healthy Iranian neonates. *Vaccine*. 2001;**19**(31):4544-8. [PubMed: [11483282](https://pubmed.ncbi.nlm.nih.gov/11483282/)].
- Rostami N, Ghaffari V, Samaie H. Comparison of immune response to hepatitis B vaccine between term and preterm infants at birth. *Arch Clin Infect Dis*. 2006;**7**(1):11-4.
- Rezaei M, Nooripoor S, Ghorbani R, Ramezanshams F, Mamishi S, Mahmoudi S. Seroprotection after hepatitis B vaccination in children aged 1 to 15 years in central province of Iran, Semnan. *J Prev Med Hyg*. 2014;**55**(1):1-3. [PubMed: [25916024](https://pubmed.ncbi.nlm.nih.gov/25916024/)]. [PubMed Central: [PMC4718339](https://pubmed.ncbi.nlm.nih.gov/PMC4718339/)].
- Hosseini SM, Ranjbar R, Abolghasemi H, Turkaman M. Evaluation of the level of HBV antibody titer after HBV vaccination among children in Tehran, Iran. *Hepat Mon*. 2009;**9**(2):150-3.
- Jafarzadeh A, Khoshnoodi J, Ghorbani S, Hazrati SM, Mazaheri BF, Shokri F. Differential immunogenicity of a recombinant hepatitis b vaccine in Iranian neonates: Influence of ethnicity and environmental factors. *Int J Infect*. 2004;**1**(2):98-104.
- Zamani A, Shajari H, Sedighy I. Study on the efficacy of recombinant hepatitis B vaccine in Iranian infants. *Med J Islamic Repub Iran*. 2001;**14**(4):347-9.
- Dahifard H. Immunogenicity of Cuban hepatitis B vaccine in Iranian children. *Arch Iranian Med*. 2004;**7**(2):89-92.
- ul Haq N, Hassali MA, Shafie AA, Saleem F, Farooqui M, Aljadhey H. A cross sectional assessment of knowledge, attitude and practice towards Hepatitis B among healthy population of Quetta, Pakistan. *BMC Public Health*. 2012;**12**:692. doi: [10.1186/1471-2458-12-692](https://doi.org/10.1186/1471-2458-12-692). [PubMed: [22917489](https://pubmed.ncbi.nlm.nih.gov/22917489/)]. [PubMed Central: [PMC3490724](https://pubmed.ncbi.nlm.nih.gov/PMC3490724/)].

26. Paganelli M, Stephenne X, Sokal EM. Chronic hepatitis B in children and adolescents. *J Hepatol.* 2012;**57**(4):885-96. doi: [10.1016/j.jhep.2012.03.036](https://doi.org/10.1016/j.jhep.2012.03.036). [PubMed: [22634122](https://pubmed.ncbi.nlm.nih.gov/22634122/)].
27. Yen YH, Chen CH, Wang JH, Lee CM, Changchien CS, Lu SN. Study of hepatitis B (HB) vaccine non-responsiveness among health care workers from an endemic area (Taiwan). *Liver Int.* 2005;**25**(6):1162-8. doi: [10.1111/j.1478-3231.2005.01157.x](https://doi.org/10.1111/j.1478-3231.2005.01157.x). [PubMed: [16343067](https://pubmed.ncbi.nlm.nih.gov/16343067/)].
28. de la Hoz F, Perez L, de Neira M, Hall AJ. Eight years of hepatitis B vaccination in Colombia with a recombinant vaccine: factors influencing hepatitis B virus infection and effectiveness. *Int J Infect Dis.* 2008;**12**(2):183-9. doi: [10.1016/j.ijid.2007.06.010](https://doi.org/10.1016/j.ijid.2007.06.010). [PubMed: [17913535](https://pubmed.ncbi.nlm.nih.gov/17913535/)].
29. Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, et al. Evaluation of the impact of hepatitis B vaccination among children born during 1992-2005 in China. *J Infect Dis.* 2009;**200**(1):39-47. doi: [10.1086/599332](https://doi.org/10.1086/599332). [PubMed: [19469708](https://pubmed.ncbi.nlm.nih.gov/19469708/)].
30. Poorolajal J, Mahmoodi M, Majdzadeh R, Nasser-Moghaddam S, Haghdoost A, Fotouhi A. Long-term protection provided by hepatitis B vaccine and need for booster dose: a meta-analysis. *Vaccine.* 2010;**28**(3):623-31. doi: [10.1016/j.vaccine.2009.10.068](https://doi.org/10.1016/j.vaccine.2009.10.068). [PubMed: [19887132](https://pubmed.ncbi.nlm.nih.gov/19887132/)].