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Hepatitis B Virus Infection in Vaccinated Children and Adolescents with HBsAg-positive Parents: Is Routine Vaccination Sufficient?

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Abstract

Background: Hepatitis B virus (HBV) is a severe public health problem in Iran. This study was conducted to investigate the intrafamilial transmission of HBV in vaccinated children whose one or both parents were positive for hepatitis B surface antigen (HBsAg).
Methods: In a study with retrospective cohort design, 110 exposed cases with HBsAg-positive parent(s) were compared with 110 unexposed controls of the same sex and age groups. The participants were directly asked about demographic characteristics, medical history, and vaccinations. Blood samples were collected and analyzed for HBV infection markers using the ELIZA method.
Results: Overall, 1.8% HBsAg ($P = 0.15$) and 13.6% hepatitis B core antibody (HBcAb) ($P < 0.0001$) positivity rates were detected in the exposed group. The hepatitis B surface antibody titer (HBsAb) showed that 34.5% of cases and 56.3% of controls had HBsAb levels > 10 IU/L. There was a significant difference in the protective HBsAb level between the two groups ($P < 0.0001$). There were significant associations between HBsAb level and gender in the exposed group and decreased HBsAb levels and age.
Conclusions: The high rate of positive HBcAb and HBsAg and decreasing HBsAb levels with age in this study indicate that routine childhood vaccination programs are inadequate in preventing HBV transmission and vaccine routes changing or further booster vaccination is essential. Effective case finding in vaccinated children with HBsAg-positive parents, intradermal vaccination, and hepatitis B immunoglobulin in newborns with HBsAg-positive fathers are suggested.

Keywords: Adolescents, Children, Hepatitis B, Intrafamilial Transmission

1. Background

Hepatitis B virus (HBV) causes acute and chronic viral infections of the liver affecting many people worldwide. The World Health Organization (WHO) estimates that 296 million people were living with chronic hepatitis B (CHB) infection in 2019, with 1.5 million new infections per year. In 2019, hepatitis B resulted in an estimated 820,000 deaths, mostly from cirrhosis and hepatocellular carcinoma (1). According to a recent meta-analysis of survey studies, in Iran, which is in the intermediate HBV zone, the prevalence of hepatitis B was nearly 2 - 8% (2, 3). The prevalence of hepatitis B in the general population ranges from 0.87 to 8.86% in different provinces of Iran (3), and perinatal transmission and IV drug abuse are considered the main transmission routes (4).

Several routes transmit the hepatitis B virus: sharing needles or syringes for drug injections, contact with HBV-positive blood or body fluids, sexual activity, from mother to fetus (vertically), and among children in a household (horizontally) (5). The household transmission of HBV is a serious health problem. The prevalence rate of HBV infection within the carrier's family is estimated to be 5 to 50% (6, 7), and they are classified in the high-risk group for hepatitis B vaccination (8). Horizontal transmission is the main route of virus transmission in Iran, and most chronic carriers are asymptomatic, with another chronic carrier in their family (9). For this reason, it is strongly recommended that household members of HBV-positive carriers undergo annual HBsAb testing and receive a booster dose of hepatitis B vaccine when the HBsAb level falls to <10 IU/L (8). In Iran, pregnant women are tested for HBsAg, and newborns of HBsAg-positive mothers receive hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine (10). The HBV vaccination program for newborns was introduced in Iran in 1993. The hepatitis B vaccine of each type should be injected at least three times at 0, 1, and 6-month intervals via the intramuscular route (11). The cri-

terion for immunization in HBV vaccination is the appearance of an adequate concentration of antibodies to HBsAg (HBsAb) in serum in an amount of at least 10 IU/L. The higher the antibody produced, the better the resulting immunity (12). One study found a significant negative association between response to the vaccine and age (13).

Although there is already an effective vaccination program and good vaccination coverage, HBV remains a global health problem, and new cases and deaths are reported worldwide (14). Considering that HBV can be eliminated, the study of transmission routes is one of the priorities to identify the risk factors for the spread in targeted populations. Assessment of immunogenicity and immunity duration is critical to control the disease in any country, especially in endemic areas (15). The efficacy of the hepatitis B vaccine in children who have one or both parents with chronic hepatitis B remains unclear. Furthermore, considering that Iran is an intermediate endemic region for HBV infection, the importance of the program to control this infection becomes even more evident when most HBV-positive patients are asymptomatic carriers in the community (16). Although intrafamilial transmission of HBV has been studied in several regions, the study in different areas can provide valuable information about the routes of HBV transmission in the population and help to identify the main routes of intrafamilial HBV spread and local characteristics.

2. Objectives

Given the seroprevalence of HBsAg positivity in Zahedan City (17), the current study aimed to evaluate the HBV status and efficacy of routine HBV vaccination among children aged 1 - 16 years whose one or both parents were positive for HBsAg.

3. Methods

The current study with a retrospective cohort design was conducted in a university-affiliated hospital in Zahedan, southeast Iran. The study was conducted in children aged 1 to 16 years and matched controls. The subjects' parents were invited, and the trained study staff conducted a face-to-face interview to describe the research process and objectives. They all signed the informed consent form when they agreed to participate in the study. Children and adolescents were enrolled in the study only with the consent of their parents. The Ethics Committee of Zahedan University of Medical Sciences gave ethical approval according to the Declaration of Helsinki.

The exposed group included children with chronic HBsAg-positive parent(s), who were compared with unexposed subjects with healthy parents. According to previous studies, the prevalence of HBsAg positivity in the Iranian population was about 3.5% (18). Taking this prevalence rate into account, and according to $\alpha = 0.05$, P = 85%, and d = 0.05, the sample size was calculated to be 196 participants; however, the present study enrolled 220 participants (110 exposed cases and 110 unexposed controls). The sample size was measured using the following formula for sample calculation:

$$\begin{aligned} Sample\ size &= \frac{Z^2_{\frac{\alpha}{2}} \times P\,(1-P)}{d^2} \\ &= \frac{(1.96)^2 \times 0.85\,(1-0.85)}{(0.05)^2} \\ &\cong 195.92 \end{aligned}$$

Couples with HBsAg positivity were recruited from the outpatient department of internal medicine during their routine case investigations. We aimed to compare each exposed case with control participants of the same sex and age groups (1 - 5, 6 - 10, and 11 - 16 years). Inclusion criteria for exposed cases were having parent(s) with chronic HBV infection, complete vaccination against hepatitis B under the routine national childhood vaccination programs in Iran, native Persian language, and completion of the informed consent form. Exclusion criteria were unvaccinated children, lack of documentation for HBV vaccination, and other viral liver infections in parents and their children (such as hepatitis C virus, etc.). As unexposed controls, vaccinated children of couples with no current and/or previous HBV infection signing the informed consent form were included in the study.

Blood samples (5 cc) were collected from each participant, and data on sex, birth date, and medical and immunological history were gathered using a questionnaire. Complete HB immunization was defined as the full administration of three doses of the hepatitis B vaccine; the vaccination status was determined from the vaccination card.

The blood samples were then tested at the Blood Transfusion Organization Laboratory and analyzed for HBV markers using the ELISA method (Dade Behring Kit). The HBV markers for which the serum was tested included hepatitis B core antibody (HBcAb), hepatitis B surface antigen (HBsAg), and hepatitis B surface antibody titer (HBsAb). An HBsAb level of $\geq$ 10 IU/L was considered protective against HBV infection.

The data were analyzed using SPSS for Windows® version 16.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics (eg, mean, percentage, standard deviation, and frequency) were measured. In addition, a comparison between groups was made using the chi-square test and relative risk (RR)

with 95% confidence interval (CI), appropriately. The significance level was set at 0.05, and the statistician was blind to the study.

4. Results

In general, the exposed HBV group included 53 (48.2%) males and 57 (52.8%) females, and the unexposed group included 54 (49.1%) males and 56 (51.9%) females. In the unexposed group, most of the children were in the age group of 6 - 10 years, and the least were in the age group of 10 - 16 years. In the exposed HBV group, the percentage of children in the age groups was similar.

The prevalence rates of HBsAb, HBcAb, and HBsAg in adolescent children with HBsAg-positive parents in exposed and unexposed control groups are shown in Table 1. In the unexposed group, HBsAg and HBcAb were negative. In the exposed HBV group, HBsAg was positive in 1.8% of the samples. The prevalence of HBcAb positivity in the exposed group was 13.6%.

In addition, the prevalence of HBsAb in different gender and age subgroups of participants was evaluated.

Table 2 shows a significant association between HBsAb level and gender in the HBV group. There was also a significant association between decreased HBsAb levels and age.

Table 3 shows the relative frequency distribution of HBsAb levels in subjects based on active or inactive chronic hepatitis B of HBsAg-positive parents compared with controls.

5. Discussion

The current study aimed to measure the efficacy of the hepatitis B vaccine in intrafamilial transmission in children whose parent(s) had chronic hepatitis B. The main findings of the present study are (1) HBsAg and HBcAb were positive in 1.8% and 13.6%, respectively, in the HBV-exposed group; (2) there was a significant difference in HBsAb level between HBV-exposed and non-exposed groups; (3) there was a significant association between HBsAb level and gender in the HBV group; (4) there was a significant association between decreased HBsAb level and older age, and (5) there was no significant difference between subgroups (active and inactive chronic hepatitis) of affected parents In terms of HBsAb level. The results of this study have important implications for HBV high-risk groups.

Our results are consistent with the medical literature showing that family members of HBsAg-positive carriers are at increased risk of infection (19) and that vaccine-induced immunity declines with age (20). Both parent-to-child and sibling-to-sibling horizontal transmission could be the main route for the intrafamilial spread of HBV infection, with the maternal route predominating (21). In a study conducted in Turkey, Barut et al. reported that among cases with HBsAg-positive parents, the rate of infected cases (HBsAg+, HBsAb-) was 14.4%, that of uninfected individuals (HBsAg-, HBsAb-) was 38.4%, and that of vaccinated individuals (HBsAg-, HBsAb+) was 5.3% (22). It has been reported that the HBsAg positivity rate in children whose mothers were HBsAg-positive was also high in the age groups of 11 - 20 years and over 21 years (23). Conversely, infected fathers were the main reservoirs of infection in our study, leading to horizontal transmission. Our finding suggests that immunoprophylaxis with HBIG should also be considered in HBsAg-positive fathers to prevent vertical transmission to newborns of HBsAg-positive mothers, and all infants should have adequate immunity to HBV demonstrated by serological markers. If a high-risk child (with HBsAg-positive parents) does not respond to routine vaccination, it is better to administer the vaccine intradermally rather than intramuscularly or at a higher dose (see below).

Susceptibility to HBV infection is known to increase with age and in men (24). Consistent with the relevant literature, our results showed a significantly lower HBsAb level in male subjects in the HBV group. Decreased HBsAb level in participants with HBsAg-positive parents may indicate their susceptibility and genetic influence on HBV infection markers (25).

Our results showed that 13.6% of family members of HBsAg-positive carriers in the HBV-exposed group were HBcAb-positive. Isolated HBcAb demonstrates removed infection and explains that routine vaccination is insufficient and results in occult HBV infection, raising concerns about HBV transmission and an association with hepatocellular carcinoma (26). Therefore, the high rate of isolated HBcAb in our study reflects the high incidence of HBV infection with intrafamilial exposure and failure of routine vaccination. In a 2019 study in Iran, Ghaziasadi et al. reported that HBsAb > 10 IU/L was 45.7% in vaccinated children from a subgroup of the general population with parents of occult hepatitis B infection positivity and HBsAb < 10 IU/L was 54.3%. Moreover, 16% of vaccinated children were positive for occult hepatitis B infection (27). In another study conducted in Iran, the markers of HBV infection were detected in about 30% of vaccinated children whose mothers were seropositive for HBsAg, and the rate of chronic carriers was measured at 14.4% (28). This high rate highlights the importance of more effective case finding and immunization programs (booster doses or other routes of vaccination) in families with HBsAg-positive members.

This study supports the notion that the current protocol enforced in countries such as Iran, which man-

Table 1. Prevalence of HBsAg, HBsAb, and HBcAb in Exposed and Unexposed Groups [a, b]

	Unexposed (N = 110)		Exposed (N = 110)		P-Value	RR	95% CI
	Positive	Negative	Positive	Negative			
HBsAg	0	110 (100)	2 (1.8)	108 (98.2)	0.15	-	-
HBsAb	62 (56.3)	48 (43.6)	38 (34.5)	72 (65.4)	< 0.0001 [c]	0.41	0.26 - 0.62
HBcAb	0	110 (100)	15 (13.6)	95 (86.4)	< 0.0001 [c]	-	-

Abbreviations: HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBcAb, hepatitis B core antibody.
[a] Values are expressed as No. (%).
[b] Chi-square test and relative risk (RR) with 95% confidence interval (CI) were used.
[c] Significant

Table 2. Frequency of HBsAb Levels, Gender, and Age in Exposed HBV and Unexposed Control Groups

Groups	HBsAb, No. (%)		P-Value [a]
	< 10 (IU/L)	> 10 (IU/L)	
Gender			
Unexposed			0.32
Female	21 (38.89)	33 (61.11)	
Male	27 (48.21)	29 (51.79)	
Exposed			< 0.0001 [b]
Female	32 (60.37)	21 (39.63)	
Male	40 (70.18)	17 (29.82)	
Age (y)			
Unexposed			< 0.0001 [b]
1 - 5	19 (46.34)	22 (53.66)	
6 - 10	26 (60.47)	17 (39.53)	
11 - 16	15 (57.69)	11 (42.31)	
Exposed			< 0.0001 [b]
1 - 5	11 (28.95)	27 (71.05)	
6 - 10	7 (18.92)	30 (81.08)	
11 - 16	14 (40.00)	21 (60.00)	

Abbreviations: HBV, hepatitis B virus; HBsAb, hepatitis B surface antibody; IU/L, international units per liter.
[a] Chi-square test was used.
[b] Significant

dates hepatitis vaccination for high-risk children, is inadequate (28). Based on the low rate of infection in the unexposed group, parent-to-child transmission is the most likely route of infection in exposed children. Therefore, the urgency of routine maternal and paternal screening and case finding in children with HBsAg-positive parents must be emphasized. Although there is nothing to prevent the continuation of routine vaccination in newborns, further booster doses of hepatitis B vaccination should be given after the initial vaccination to prevent HBV infection in vaccinated healthy individuals with household members of HBV-positive carriers based on serological surveillance (8). It has been suggested that a vaccine dose should be administered in early adolescence, as this may provide longer-term protection into adulthood (29). In addition, many literature data suggest that intradermal vaccination against hepatitis B improves seroconversion rates in patients who do not respond to vaccination. In a previous study, the seroconversions of 63%, 100%, and 96% were observed with subcutaneous (2 micrograms), intradermal (2 micrograms), and intramuscular (20 micrograms) administration of hepatitis B vaccine, respectively (30). Proper intradermal administration of the vaccine is critical for an adequate immune response. Therefore, intradermal vaccines appear to be an effective alternative to other routes in immunization programs in families with HBsAg-positive members. Improving population knowledge (31) of HBV risk factors, vaccination, and transmission in high-risk groups could reduce parent-to-child transmission.

The present study had some limitations. We could not determine vertical transmission from mother during delivery, and there was no medical documentation about HBIG administration to infants of HBsAg-positive mothers in the past; however, the number of HBsAg-positive mothers in the exposed group was low (17.27%), and some of them had been administrated HBIG. In our study, many infected children had infected fathers, suggesting that they may have a polymorphism making them susceptible to HBV infection. In addition, we did not test HBV DNA in HBsAg-negative subjects, although occult HBV infections are rarely reported in HB-vaccinated infants, especially at low HBsAb levels. The results of this study have significant implications for clinical practice, so we suggest implementing other routes of HBV vaccination (intradermal) or booster doses among HBV-vaccinated children with HBV-carrier parents to reduce HBV transmission in high-risk groups.

In conclusion, the high HBcAb rate among children with HBV carrier parents and decreasing HBsAb levels with age in this study highlight the inadequate prevention of

Table 3. Relative Frequency Distribution of HBsAb Levels in Exposed Subjects with Carrier Parents Compared with Unexposed Controls

Positive for HBV	HBsAb, No. (%)		P-Value [a]
	< 10 (IU/L)	> 10 (IU/L)	
Unexposed			-
None	36 (32.72)	74 (67.28)	
Exposed			0.53
Inactive CHB father	11 (35.48)	20 (64.52)	
Inactive CHB mother	5 (38.46)	8 (14.8)	
Active CHB father	14 (23.33)	46 (76.67)	
Active CHB mother	2 (33.33)	4 (66.67)	

Abbreviations: HBV, hepatitis B virus; HBsAb, hepatitis B surface antibody; IU/L, international units per liter; CHB, chronic hepatitis B.
[a] Chi-square test was used. $P < 0.05$ was significant.

HBV transmission by childhood vaccination and the importance of vaccine routes changing and further booster doses. In addition, consideration should be given to reducing intrafamilial transmission with HBIG in newborns even in HBsAg-positive fathers, more effective HBV case finding in vaccinated children with HBsAg-positive parents, and patient education.

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Footnotes

Authors' Contribution: All authors had equal roles in performing research and writing the paper.

Conflict of Interests: The authors declare that they have no conflicts of interest.

Ethical Approval: The present study was conducted following the Declaration of Helsinki and the ethical guidelines for medical and health research established by the Ministry of Health and Medical Education and the Ministry of Science, Research, and Technology, Iran. We obtained approval from the Ethics Committee of Zahedan University of Medical Sciences (registration number IR. ZAUMS. REC .1397.255).

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Informed Consent: The participants agreed to participate in the present study and signed consent forms. Children and adolescent subjects were included only with their parent's permission.

References

1. World Health Organization. *Interim guidance for country validation of viral hepatitis elimination*. World Health Organization; 2021.
2. 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). https://doi.org/10.5812/hepatmon.35577.
3. 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. [PubMed ID: 26933476]. [PubMed Central ID: PMC4773083]. https://doi.org/10.15171/mejdd.2016.01.
4. Roushan MR, Mohraz M, Velayati AA. Possible transmission of hepatitis B virus between spouses and their children in Babol, Northern Iran. *Trop Doct*. 2007;**37**(4):245–7. [PubMed ID: 17988497]. https://doi.org/10.1258/004947507782332856.
5. M A, Au Z, Su D. Epidemiology, virology, transmission, clinical manifestation and vaccine for hepatitis virus B: a review. *J Vaccines Vaccin*. 2018;**5**(3). https://doi.org/10.15406/ijvv.2018.05.00103.
6. Siddique AB, Uddin MN, Das KK, Biswas RSR. Seropositivity of HBV HCV among the Family Members of Chronic Viral Hepatitis Patients. *medRxiv*. 2021. https://doi.org/10.1101/2021.05.12.21257115.
7. Thakur V, Kazim SN, Guptan RC, Malhotra V, Sarin SK. Molecular epidemiology and transmission of hepatitis B virus in close family contacts of HBV-related chronic liver disease patients. *J Med Virol*. 2003;**70**(4):520–8. [PubMed ID: 12794713]. https://doi.org/10.1002/jmv.10426.
8. Wilkins T, Sams R, Carpenter M. Hepatitis B: screening, prevention, diagnosis, and treatment. *Am Fam Physician*. 2019;**99**(5):314–23.
9. Zali MR, Shalmani HM. The changing epidemiology of hepatitis B in Iran. *Gastroenterol Hepatol Bed Bench*. 2010;**3**(1).
10. Navabakhsh B, Mehrabi N, Estakhri A, Mohamadnejad M, Poustchi H. Hepatitis B virus infection during pregnancy: transmission and prevention. *Middle East J Dig Dis*. 2011;**3**(2):92–102.
11. 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. [PubMed ID: 25077146]. [PubMed Central ID: PMC4114169]. https://doi.org/10.4103/2277-9531.134741.
12. Zanetti AR, Mariano A, Romanò L, D'Amelio R, Chironna M, Coppola RC, et al. Long-term immunogenicity of hepatitis B vaccination and policy for booster: an Italian multicentre study. *Lancet*. 2005;**366**(9494):1379–84. https://doi.org/10.1016/s0140-6736(05)67568-x.

13. Jouneghani AS, Chaleshtori MH, Khoshdel A, Kheiri S, Farrokhi E, Khalafian P, et al. Evaluation of response to hepatitis B vaccine in Iranian 6-18-year-old students. *J Res Med Sci*. 2017;**22**:116. [PubMed ID: 29184574]. [PubMed Central ID: PMC5680656]. https://doi.org/10.4103/jrms.JRMS_204_17.
14. World Health Organization. *Progress report on HIV, viral hepatitis and sexually transmitted infections 2019: accountability for the global health sector strategies, 2016-2021*. World Health Organization; 2019.
15. Chen DS. Hepatitis B vaccination: The key towards elimination and eradication of hepatitis B. *J Hepatol*. 2009;**50**(4):805–16. [PubMed ID: 19231008]. https://doi.org/10.1016/j.jhep.2009.01.002.
16. Attaran MS, Hosseini SM, Fakhari J, Sharifi Z. Serological and molecular characterization of hepatitis B virus in asymptomatic blood donors in Iran. *Iran J Microbiol*. 2018;**10**(1):59.
17. 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. [PubMed ID: 23087764]. [PubMed Central ID: PMC3475139]. https://doi.org/10.5812/hepatmon.6618.
18. 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 ID: 22829987]. [PubMed Central ID: PMC3398635].
19. El-Shabrawi M, Abdelgawad M, Elgaddar O, Hassanin F, Khalil A, Mahfouz A, et al. A clinical and immunological study of children with chronic hepatitis B virus infection. *Prz Gastroenterol*. 2019;**14**(3):211–6. [PubMed ID: 31649794]. [PubMed Central ID: PMC6807666]. https://doi.org/10.5114/pg.2019.88171.
20. Wang X, Chen Q, Li H, Wang C, Hu L, Yang Q, et al. Asymptomatic hepatitis B carriers who were vaccinated at birth. *J Med Virol*. 2019;**91**(8):1489–98. [PubMed ID: 30883792]. https://doi.org/10.1002/jmv.25461.
21. Kanji JN, Penner RED, Giles E, Goodison K, Martin SR, Marinier E, et al. Horizontal Transmission of Hepatitis B Virus From Mother to Child Due to Immune Escape Despite Immunoprophylaxis. *J Pediatr Gastroenterol Nutr*. 2019;**68**(5):e81–4. [PubMed ID: 30889137]. [PubMed Central ID: PMC6510327]. https://doi.org/10.1097/MPG.0000000000002318.
22. Barut HS, Gunal O, Goral A, Etikan I. [Prevalence of hepatitis B virus infection in children of HBsAg positive parents]. *Mikrobiyol Bul*. 2011;**45**(2):359–65. [PubMed ID: 21644080].
23. Barut HS, Günal Ö, Göral A, Etikan I. Prevalence of hepatitis B virus infection in children of HBsAg positive parents. *Mikrobiyoloji bulteni*. 2011;**45**(2):359–65.
24. Custer B, Sullivan SD, Hazlet TK, Iloeje U, Veenstra DL, Kowdley KV. Global epidemiology of hepatitis B virus. *J Clin Gastroenterol*. 2004;**38**(10 Suppl 3):S158–68. [PubMed ID: 15602165]. https://doi.org/10.1097/00004836-200411003-00008.
25. Jiang DK, Ma XP, Yu H, Cao G, Ding DL, Chen H, et al. Genetic variants in five novel loci including CFB and CD40 predispose to chronic hepatitis B. *Hepatology*. 2015;**62**(1):118–28. [PubMed ID: 25802187]. https://doi.org/10.1002/hep.27794.
26. Miura Y, Shibuya A, Adachi S, Takeuchi A, Tsuchihashi T, Nakazawa T, et al. Occult hepatitis B virus infection as a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C in whom viral eradication fails. *Hepatol Res*. 2008;**38**(6):546–56. [PubMed ID: 18179561]. https://doi.org/10.1111/j.1872-034X.2007.00316.x.
27. Ghaziasadi A, Fakhari Z, Aghcheli B, Poortahmasebi V, Farahmand M, Norouzi M, et al. High prevalence of occult hepatitis B infection (OBI) among healthy children and their parents in Alborz province, Iran; Vertical OBI, myth or truth? *Liver Int*. 2020;**40**(1):92–100. [PubMed ID: 31518482]. https://doi.org/10.1111/liv.14252.
28. Adibi P, Ghassemian R, Alavian S, Ranjbar M, Mohammadalizadeh AH, Nematizadeh F, et al. Effectiveness of hepatitis B vaccination in children of chronic hepatitis B mothers. *Saudi Med J*. 2004;**25**(10):1414–8.
29. Pileggi C, Papadopoli R, Bianco A, Pavia M. Hepatitis B vaccine and the need for a booster dose after primary vaccination. *Vaccine*. 2017;**35**(46):6302–7. [PubMed ID: 28988867]. https://doi.org/10.1016/j.vaccine.2017.09.076.
30. Filippelli M, Lionetti E, Gennaro A, Lanzafame A, Arrigo T, Salpietro C, et al. Hepatitis B vaccine by intradermal route in non responder patients: an update. *World J Gastroenterol*. 2014;**20**(30):10383. [PubMed ID: 25132754]. [PubMed Central ID: PMC4130845]. https://doi.org/10.3748/wjg.v20.i30.10383.
31. Brouard C, Gautier A, Saboni L, Jestin C, Semaille C, Beltzer N, et al. Hepatitis B knowledge, perceptions and practices in the French general population: the room for improvement. *BMC Public Health*. 2013;**13**:576. [PubMed ID: 23764171]. [PubMed Central ID: PMC3849746]. https://doi.org/10.1186/1471-2458-13-576.