Medical Science

pISSN 2321–7359; eISSN 2321–7367

Evaluation of infection and immunity in children of mothers with HBS antigen

Manijeh Jozpanahi[1], **Zahra Hatami**[2], **Samira Akbarieh**[3], **Pegah Saeed**[2], **Nooshin Jalili**[4*]

To Cite:
Jozpanahi M, Hatami Z, Akbarieh S, Saeed P, Jalili N. Evaluation of infection and immunity in children of mothers with HBS antigen. Medical Science, 2022, 26, ms173e2095.
doi: https://doi.org/10.54905/disssi/v26i123/ms173e2095

Authors' Affiliation:
[1]Department of Infectious Disease, Zanjan University of Medical Sciences, Zanjan, Iran
[2]MD, Zanjan University of Medical Sciences, Zanjan, Iran
[3]Department of Infectious Disease, Ardabil University of Medical Sciences, Ardabil, Iran
[4]Pulmonologist, Department of Internal Medicine, Zanjan University of Medical Sciences, Zanjan, Iran; Email: nooshinjalili90@gmail.com

[*]**Corresponding Author:**
Nooshin Jalili, Pulmonologist, Department of Internal Medicine, Zanjan University of Medical Sciences, Zanjan, Iran;
Email: dr.nooshinjalili@zums.ac.ir

Contact Information

Fawwaz Farih Alshammarie	fawwzf@yahoo.com
Wael Saleh Alanazi	drwaelalanazi1@gmail.com
Sara Abdullah Aledaili	saraaledaili@gmail.com
Turki Saad Aljuhani	Aljuhani.turkisaad@gmail.com
Faisal Fahad Alshammari	Dr.fisal20@gmail.com

Peer-Review History
Received: 01 February 2022
Reviewed & Revised: 03/February/2022 to 02/May/2022
Accepted: 03 May 2022
Published: 15 May 2022

Peer-review Method
External peer-review was done through double-blind method.

URL: https://www.discoveryjournals.org/medicalscience

ABSTRACT

Introduction: One of the main chronic diseases in developing countries is Hepatitis B, which is of particular importance due to the underlying cirrhosis of the liver and hepatocellular carcinoma. Therefore, this study was conducted to evaluate the incidence and immunity of children of mothers with hepatitis B. *Material and Methods:* The present study as a cross-sectional one was performed on HBsAg positive mothers referred to Suhrawardi Infectious Diseases Clinic in Zanjan, Iran, February 2008 to September 2020, during 12 years. In our study 129 medical records of HBsAg-positive mothers referred to the Infectious Diseases Clinic were reviewed and the extent of infection and immunity of their children were analyzed according to various factors such as maternal age, maternal gravid A, and mother HbeAg, as well as receiving or not receiving vaccine and neonatal immunoglobulin. *Results:* Achieved data from the present study revealed that 76.1% of the offspring of mothers with hepatitis B had a level of protective antibody above 10 international units. Furthermore, 94.1% of vaccine recipients with HbeAg-negative mothers showed a level of protective antibody at least above 10 international units. In children of mothers with HbeAg positive, this rate was 42.9%. In both offspring of both HbeAg positive and negative mothers, the response rate in both vaccine and immunoglobulin recipients were 100% (positive). *Conclusion:* Among vaccine recipients alone, 94.1% and 42.9% of offspring of HBeAg-negative and -positive mothers were immune. While both vaccine and immunoglobulin recipients had 100% immunity in both groups.

Keywords: Antigen, Hepatitis B, Mother.

1. INTRODUCTION

Hepatitis B is so prevalent that it has affected more than 240 million people worldwide, nearly 0.25% of which die every year because of acute or chronic forms of this disease (Dhouib et al., 2020). Based on the reported data from previous studies, Hepatitis B is one of the most serious health problems in Iran which is rated as the tenth leading cause of death in this country (Khodaveisi et al., 2010). Hepatitis B could be prevented by vaccination as one of the most impressive remedial options, such a way clinical studies have revealed that the vaccine is safe and highly potent in stimulating the immune

system (Van Damme, 2016). In 1992 a universal goal was specified by the World Health Organization (WHO) based on which all the countries should prepare a vaccination program against hepatitis B by 1997 (Organization, 2020).

Vaccination of infants at birth with hepatitis B vaccine aimed to improve their immunization has a very high effect (Van Der Meeren et al., 2016). However, the duration of protection induced by this vaccine is not yet known and should be considered in long-term follow-up programs (Bruce et al., 2016). Vaccination against hepatitis surface antigen has the ability to inhibit antibody-protective levels (greater than 10 international units per liter) in most vaccinated individuals. Qawasmi et al., (2015) reported that the titer of this antibody decreases over time. Meanwhile, despite the very high impact of the vaccine, about 5 to 10% of people are unable to produce antibodies at acceptable levels against hepatitis B surface antigen (HBsAg) for a number of reasons, including genetic factors, immune suppression and some specific diseases. In the meantime, differentiating real unresponsive people (after immunization) and people with reduced antibody titers below the immunogenicity range are very important because even 10 years after vaccination, immunological memory can protect against the virus in the second group despite the low titer. However, these two groups are at risk and booster doses would be necessary in the following years (Sjogren, 2005).

The routs of hepatitis transmission are cutaneous-mucosal contact with infected blood and secretions, sexual transmission, mother to fetus transmission, and lactation (rare). Maternal-to-fetal transmission often occurs in the prenatal phase, and vertical transmission is less likely (about 10%) to occur (Bennett et al., 2014). Due to the possibility of further acquisition around delivery, prevention of this disease in the fetus is easier. By injecting HBIg in the first 12 hours of life at a dose of half a cc along with the vaccine at birth the immunity could be increased (with a separate syringe and in a separate place of immunoglobulin), (Latthaphasavang et al., 2019).

In their study, Yahyapour et al., (2009) determined the serological markers as the antibodies of hepatitis B virus in children born to HBsAg positive mothers. The result of HBsAg test among 31,241 pregnant women who gave birth within 5 years, was positive for 140 of them, of whom 123 were enrolled, all of whom had received the vaccine and immunoglobulin, and the result of HBsAg test was positive in only one child (Yahyapour, 2009). Due to the lack of accurate national statistics on prenatal hepatitis B in children born to chronically ill mothers, evaluation of the preventive effect of HBV and hepatitis B-specific immunoglobulin vaccines is very important when neonates are given at birth.

Moreover, it is crucial to compare their immunity with that of children who have received the HBV vaccine alone. The high importance of chronic carriers of hepatitis B, which has more serious and common complications in infants, is of great importance. Therefore, the main objective of this study was to assess the extent of involvement and immunity in children of mothers with HBS antigen.

2. MATERIAL AND METHODS

As a cross-sectional one, the present study was carried out on HBsAg positive mothers referred to Suhrawardi Infectious Diseases Clinic in Zanjan, Iran, February 2008 to September 2020, during 12 years. All the individuals with appropriate characteristics of inclusion criteria were included in our study. Inclusion criteria were: having informed consent, mothers with HbsAg positive. Exclusion criteria include: incomplete file of information.

Procedure

In our study, 129 medical records of HBsAg-positive mothers referred to the Infectious Diseases Clinic were reviewed and the extent of infection and immunity of their children were analyzed according to different factors including maternal age, maternal gravidA, and mother HbeAg, as well as receiving or not receiving vaccine and neonatal immunoglobulin.

Data analysis

Descriptive statistics for quantitative data were described as mean and standard deviation. For qualitative data, percentage and frequency were used by preparing related tables and graphs. Chi-square test was used in inferential statistics to determine the relationship between qualitative data. To compare the means between groups for two independent groups with normal distribution data (which is measured using Klomogorov-Smirnov test) t-test and analysis of variance were used for the two studied groups. In case of non-normally distributed data, Mann-Whitney test was used for two groups and Kruskal-Wallis test was used for several groups. For specifying the effective factors, linear regression was used in which the level of neonatal antibodies as an outcome and factors such as maternal age, gravida and underlying disease as well as HbeAg as predictor variables were entered into the model. To perform analysis in our study in more accurate way SPSS-19 software was used and a P value level of 0.05 was considered to be statistically significant.

Ethical considerations

The manager of this project kept the information of all patients of the study secret. During the research, the declarations of the research ethics committee of Helsinki and the University of Medical Sciences were considered. The project was carried out after approval by the Research Council of the Medical School and receiving the code of ethics ZUMS.REC.1395.91.

3. RESULTS

Here 129 children of HBsAg-positive mothers were evaluated, but unfortunately, 41 of them were removed from the study due to incomplete information. The frequency and percentage of maternal HbeAg, maternal HbeAb and high ALT levels were assessed. The data revealed that 21 cases (23.85%) were HbeAg positive, followed by HbeAb positive (63 cases; 71.59%), both antigen and antibody negative (1 case; 1.13%) and high maternal ALT (3 cases; 3.4%). The frequency and percentage of vaccine status by the child and the vaccine and immunoglobulin received by the child were evaluated. Our data revealed that 48 children (54.52%) received the vaccine alone and 29 children (32.95%) received immunoglobulin and the vaccine together. Also, 11 children (12.5%) did not receive any of them. In Figure 1, frequency of maternal HbeAg positive status, maternal HbeAb positive, infant immunoglobulin intake, infant vaccination, maternal high ALT in terms of maternal gravida was evaluated. The results demonstrated that 281% of mothers in Gravid 1 had HbeAg positive, along with mothers in gravida 2 (21.1%) and mothers in gravida 3 and above (83.3%).

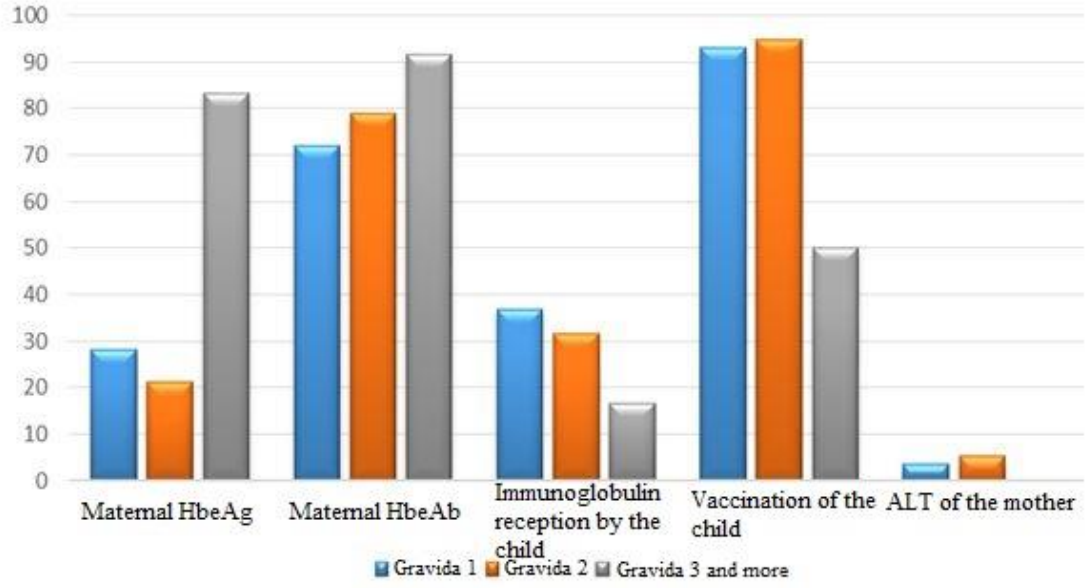

Figure 1 Frequency and percentage of maternal HbeAg and HbeAb positive status, immunoglobulin reception by the child, vaccination of the child, high ALT of the mother, in terms of maternal gravida

In Table 1, the frequency and percentage of maternal HbeAg and HbeAb positive status, infant immunoglobulin intake, infant vaccination, maternal high ALT were assessed in terms of high risk and low risk mothers based on age. Mothers under 18 and 35 years and older were in the High-Risk group. According to the results, 35.3% of high-risk mothers were positive for HbeAg and 21.4% of low-risk mothers were detected to be positive for HbeAg.

Table 1 Frequency and percentage of maternal HbeAg, HbeAb positive status, child immunoglobulin intake, child vaccination, maternal high ALT, in terms of high risk and low risk of mothers by age

Variable	Percent (Frequency)	
	High Risk	Low Risk
HbeAg positive maternal	6 (35.3%)	15 (21.4%)
HbeAb positive maternal	11 (64.7%)	55 (78.6%)
child immunoglobulin intake	0 (0%)	40 (28%)
child vaccination	13 (76.5%)	90 (63%)
maternal high ALT	1 (5.9%)	2 (2.9%)

Frequency of immunization (antibody level above 10 international units) and HBsAg positivity of offspring in terms of vaccine alone, vaccine and immunoglobulin combined or none were examined (figure 2). The results revealed that 79.2% of those receiving the vaccine alone were safe and those receiving the vaccine and immunoglobulin together showed 100% immunity. Also, the children who didn't undergo any of the immunization procedures were HBsAg positive (100%).

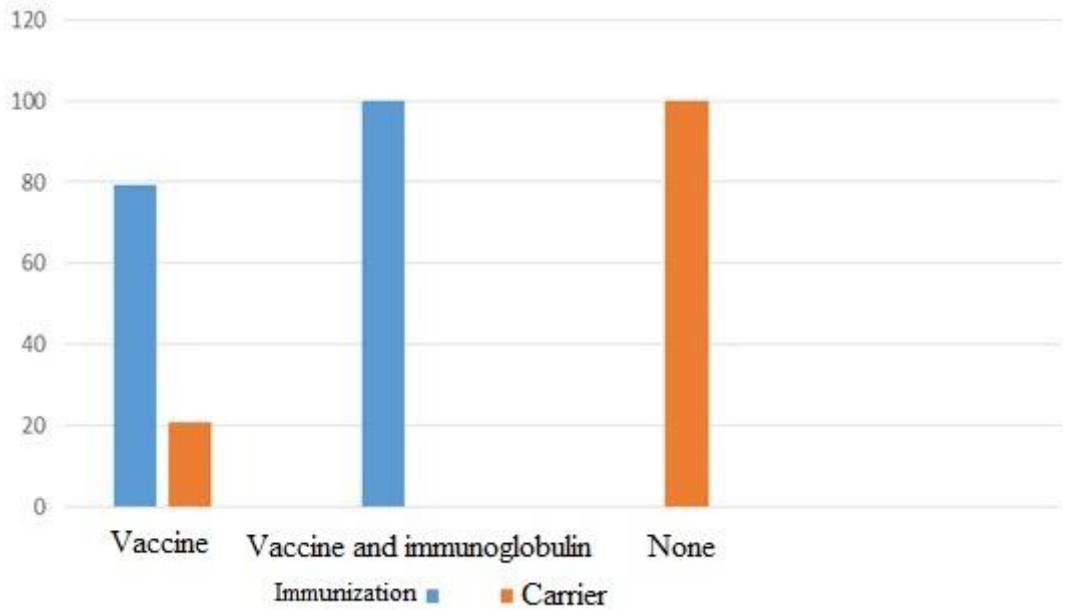

Figure 2 Frequency of immunization percentage and HBsAg positivity of offspring in terms of vaccine alone, vaccine and immunoglobulin combined or none

The frequency of immunization percentage by maternal HbeAg is represented in table (2). According to the results, 94.1% of the children whose mothers were detected with a negative HbeAg and received 2 vaccines were immunized, while this percentage was 42.9% for children of mothers with HbeAg positive. Both vaccine and immunoglobulin recipients were 100% immunized in both groups, and those who did not receive either immunization test were 100% HBsAg positive in both groups.

Table 2 Frequency of immunity of vaccine recipients alone, vaccine and immunoglobulin together or none based on the maternal HbeAg

Child safety percentage	HbeAg negative maternal	HbeAg positive maternal
Vaccine safety alone	94.1%	42.9%
Vaccine immunity + immunoglobulin	100%	100%
None	0%	0%

In multivariate statistics, by eliminating the effects of maternal age, and maternal HBeAg status, vaccine-immunoglobulin combination, showed better effects. The beta coefficients and significant levels for the correct action of the immunoglobulin and vaccine are as follows: B (standardized) = 0.551، t = 5.360 ، P-value <0.001.

4. DISCUSSION

The hepatitis B virus is amongst the most frequent cause of chronic diseases of liver cirrhosis and liver cancer around the world. Recent studies have demonstrated that more than two million people worldwide are at risk for Hepatitis B virus of which 350 million are chronic carriers of hepatitis (Bierhoff et al., 2020). 90% of children with HBsAg-positive mothers, especially if they are also HBeAg-positive, become HBsAg-positive during the first 3 months of life, and a larger part of these children would carry

chronic hepatitis B virus (Funk et al., 2021). Therefore, the objective of this study was to assess the extent of involvement and immunity in children of mothers with HBS antigen.

The data from our study demonstrated that more than three-quarters of the children whose mothers had hepatitis B were detected with a level of protective antibody above 10 international units and nearly a quarter of the offspring were HBsAg positive. Based on the data from our study, it was observed that the frequency of HBsAg positive in children whose mothers were detected with a positive HBsAg was almost twice that of HBeAg negative mothers so that the number of mothers with HBeAg positive who were detected with HBsAg in was 38.1%, while this rate was only 19.4% in the other group. Previous studies have shown that if the mother is HBeAg positive, the risk of transmission of disease to children will increase, and according to these results, the mother being HBeAg positive is the biggest risk factor for immunization failure (Zhang et al., 2014b).

The data from our study also showed that children receiving only the vaccine, and whose mothers were HBeAg positive, showed less response to the vaccine. While 94.1% of vaccine recipients with HbeAg-negative mothers showed a level of protective antibody at least above 10 international units. In children of mothers with HbeAg positive, this rate was 42.9%. This difference could be partly is related to higher infectivity rates, resulting in greater transmission power, and perhaps differences in the genetics of the viruses could be involved in maternal HbeAg positivity. In a study by Zhang et al., (2014) only 75% of children born to HBeAg-positive mothers who were vaccinated, were immunized, but all children born to HBeAg-negative mothers, who were vaccinated, were immunized.

In our study, the rate of immune response was assessed separately among three groups of children receiving the vaccine alone, those receiving the vaccine and immunoglobulin, and the remaining ones who didn't receive any of them. Based on the data presented herein, vaccine and immunoglobulin recipients showed the highest level of antibodies, so that; antibody level among them was notably higher compared to the other two groups. When these results were reproduced in multivariate statistics, vaccination and immunoglobulin still exhibited better results than vaccine alone or non-vaccination by eliminating the effects of other variables (i.e., maternal Ab level or maternal Ag positive level and child age). The results are not far-fetched, as receiving both types of immunization will provide antibodies through both vaccination and receiving antibodies directly. Degraded and antibody levels were greatly reduced in both the vaccine recipients alone and in both immunization recipients.

As a result, more time will be needed to reduce antibody levels in this category. The results of multivariate statistics were capable of confirming this (Koc et al., 2020). Studies on the combined effect of using immunoglobulin and vaccine in infants of mothers who were positive for hepatitis B virus test have shown conflicting results compared to the vaccine alone, while some human studies have not shown a greater effect on the use of either two immunizations. Other studies have evaluated the combined use of these two types of immunizations more effectively. In other word, in some studies, the effect of using immunization was considered more effective only in HbeAg-positive mothers. In general, the use of immunoglobulin for the children of mothers with positive HBsAg and negative HBeAg has shown contradictions (Zhang et al., 2014b).

The results of our study have been recommended in some countries, such as Taiwan, in which co-immunization could be recommended only for children born to mothers positive for HbeAg However, in some countries, both types of immunization are routinely recommended for HbsAg-positive mothers (Zhang et al., 2014b). Some studies considered the risk of fulminant hepatitis to be lower in both immunization recipients than in vaccine recipients alone (Zhang et al., 2014a). In Iran, the use of both immunizations is suggested for the children of all mothers with HbsAg positive. In some studies, maternal serum DNA levels were reported to have a key role in responding to active immunization or simultaneous active and inactive immunization (Zhang et al., 2014b).

In our study, 5.9% of children receiving only vaccine and with HBeAg positive became infected, while the others who were vaccinated and received immunoglobulin became immune (100%). In a study by Chen et al., (2012) offspring of HBeAg-negative mothers receiving the vaccine alone reported an involvement of 1%. Anyway, the prevalence of hepatitis B is not high in people born to HBeAg-negative mothers who only receive the vaccine (5.9%). However, even this small percentage seems to make it necessary to emphasize the simultaneous administration of vaccine and immunoglobulin. Besides, 57.1% of the children of positive HbeA mothers receiving only the vaccine, became infected with HBsAg. These findings emphasize that co-administration of immunoglobulin and vaccine in children of HBeAg-positive mothers will be an undeniable necessity. Anyway, it seems to be effective in conducting studies for evaluating the cost-effectiveness of vaccination and administration of immunoglobulin simultaneously among the children of mothers with HBeAg-negative hepatitis B.

The data from our study also revealed that 79.2% of individuals receiving the vaccine alone had HBS antibodies above 10, while this figure was 100% for those receiving the immunoglobulin vaccine. The participants who did not undergo any of the immunization procedures were found to be 100% HBS antibody negative. We also revealed that high-risk mothers in terms of age (mothers under 18 and over 35 at birth) had a higher percentage of HBeAg positive than mothers at low risk. Part of the difference

may be because mothers who become pregnant at a young or older age are usually from lower socioeconomic classes, which might indicate the low use of antiviral therapies in this group of society. Another part of the data from our study shows that the group of mothers at low risk (in terms of age) had a higher frequency of vaccination. Because the study defined the mothers older than 35 as high-risk ones, it could be expected that these people were usually of older generations when vaccination was not routinely used at the time. Perhaps the reason for lower immunoglobulin in high-risk mothers can also be related to this issue.

5. CONCLUSION

Among vaccine recipients alone, 94.1% and 42.9% of offspring of HBeAg-negative and -positive mothers were immune. While both vaccine and immunoglobulin, recipients had 100% immunity in both groups. According to the results, it is recommended to continue the national program of vaccination in both forms of active and inactivated immunization for all children of HBsAg positive mothers.

Consent for publication

All authors declare that they have Consent for publication

Authors' contributions

All authors contributed to the design of the study, as well as data collection and analysis, and the writing of the manuscript. All authors read and approved the final manuscript.

Funding

This study has not received any external funding.

Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

REFERENCES AND NOTES

1. Bennett J, Dolin R, Blaser M. Mandell, douglas, and bennett's principles and practice of infectious diseases: 2-volume set: Elsevier Health Sciences. Philadelphia, Saunders, Elsevier 2014.
2. Bierhoff M, Nelson KE, Guo N, Jia Y, Angkurawaranon C, Jittamala P, Carrara V, Watthanaworawit W, Ling C. Prevention of mother-to-child transmission of hepatitis B virus: protocol for a one-arm, open-label intervention study to estimate the optimal timing of tenofovir in pregnancy. BMJ open 2020; 10: e038123.
3. Bruce MG, Bruden D, Hurlburt D, Zanis C, Thompson G, Rea L, Toomey M, Townshend-Bulson L, Rudolph K. Antibody levels and protection after hepatitis B vaccine: results of a 30-year follow-up study and response to a booster dose. J Infect Dis 2016; 214: 16-22.
4. Chen HL, Lin LH, Hu FC, Lee JT, Lin WT, Yang YJ, Huang FC, Wu SF, Chen SC. C. Effects of maternal screening and universal immunization to prevent mother-to-infant transmission of HBV. Gastroenterol 2012; 142: 773-781.
5. Dhouib W, Kacem M, Bennasrallah C, Fredj MB, Abroug H, Zemni I, Chelly S, Maalel I, Samia GS. Hepatitis B birth vaccination, cohort study, Tunisia 2000–2017. Libyan J Med 2020; 15.
6. Funk AL, Lu Y, Yoshida K, Zhao T, Boucheron P, Van Holten J, Chou R, Bulterys M. Efficacy and safety of antiviral prophylaxis during pregnancy to prevent mother-to-child transmission of hepatitis B virus: a systematic review and meta-analysis. Lancet Infect Dis 2021; 21: 70-84.
7. Khodaveisi M, Mohammadi N, Omidi MSA, Amini R. Antibody Titers of Hepatitis B in Hamadan's Nursing and Midwifery Students. Avicenna J Nurs Midwifery Care 2010; 18, 45-55.
8. Koc ÖM, Menart C, Theodore J, Kremer C, Hens N, Koek GH. Ethnicity and response to primary three-dose hepatitis B vaccination in employees in the Netherlands, 1983 through 2017. J Med Virol 2020; 92, 309-316.
9. Latthaphasavang V, Vanhems P, Ngo-Giang-Huong N, Sibounlang P, Paboriboune P, Malato L, Keoluangkhot V, Thammasack S, Salvadori N. Perinatal hepatitis B virus transmission in Lao PDR: a prospective cohort study. PLoS One 2019; 14: e0215011.
10. Organization WWH. Key facts _ Hepatitis B. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b 2020
11. Qawasmi M, Samuh M, Glebe D, Gerlich Wh, Azzeh M. Age-dependent decrease of anti-HBs titers and effect of booster doses using 2 different vaccines in Palestinian

children vaccinated in early childhood. Hum Vaccin Immunother 2015; 11: 1717-1724.
12. Sjogren MH. Prevention of hepatitis B in non-responders to initial hepatitis B virus vaccination. Am J Med 2005; 118: 34-39.
13. Van Damme P. Long-term protection after hepatitis B vaccine. Oxford University Press 2016.
14. Van Der Meeren O, Behre U, Crasta P. Immunity to hepatitis B persists in adolescents 15–16 years of age vaccinated in infancy with three doses of hepatitis B vaccine. Vaccine 2016; 34: 2745-2749.
15. Yahyapour YKM, Kheir N, Hashemzade Omran A, Jazayeri Sm, Saadatmand Z. Determining serological markers of hepatitis B virus in infants born to HBsAg-positive mothers. J Gorgan uni 2009; 11: 43-48.
16. Zhang L, Gui X, Wang B, Ji H, Yisilafu R, Li F, Zhou Y, Zhang L, Zhang H. A study of immunoprophylaxis failure and risk factors of hepatitis B virus mother-to-infant transmission. Eur J Pediatr 2014; 173: 1161-1168.
17. Zhang L, Gui XE, Teter C, Zhong H, Pang Z, Ding L, Li F, Zhou Y. Effects of hepatitis B immunization on prevention of mother-to-infant transmission of hepatitis B virus and on the immune response of infants towards hepatitis B vaccine. Vaccine 2014; 32: 6091-6097.