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Research Article

Factors Affecting the Long-Term Protection Against Hepatitis B Immunization in Infancy: A Meta-Analysis

Aldila Pratiwi[1], Bagus Setyoboedi[1,*], Citrawati D. K. Wungu[2]

ABSTRACT

Introduction: Hepatitis B virus (HBV) infection is a major global health issues and one of the most dangerous viral infections with a high mortality rate. Newborns and infant vaccination against chronic HBV infection are crucial for preventing mother-to-child transmission (MTCT). This study aimed to conduct a meta-analysis to investigate the factors affecting long-term protection against Hepatitis B Immunization in infancy. **Material and Methods**: Our literature searches are from PubMed, Science Direct, Web of Science, and ProQuest publications between January 2000 and December 2021. The included literature assessed the risk of bias using the Newcastle Ottawa Quality Assessment Scale. We identify Hepatitis B surface antibodies (anti-HBs) ≥ 10 mIU/mL as being protective against HBV infection. The results are combined with a random effect or fixed effect model. **Results**: Eighteen eligible observational studies with a total of 16,642 participants were included. Analysis of factors affecting long-term protection status by assessing anti-HBs titers showed significant results on several factors, including gestational age for anti-HBs titers (OR 2.5; 95% CI 1.62-3.85; p<0.0001), weight for age to anti-HBs titers (OR 1.36; 95% CI 1.06-1.75; p=0.02), length for age to anti-HBs titers (OR 0.01; 95% CI 0.01-0.02; p<0.00001), and immunization status based on the number of vaccine doses (4 doses vs 3 doses) to anti-HBs titers (p<0.00001). **Conclusions**: Anti-HBs titers of hepatitis B immunization were significantly affected by gestational age, weight for age, length for age, and vaccine doses. Parents of newborns must be informed about basic immunization and provide adequate nutritional intake to the mother and babies to prevent HBV infection.

Key words: Hepatitis B antibodies, Hepatitis B vaccines, Immunity, Immunization, Infant.

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INTRODUCTION

Hepatitis B virus (HBV) infection is still one of the most dangerous viral infections in humans, with a high mortality rate. HBV infection causes 1.2 million people to die each year from chronic.[1] HBV infection continues to be a serious global health issue.[2-4] One of the HBV infection transmissions, known as mother-to-child transmission (MTCT) or vertical transfer, can happen during pregnancy.[5] To stop the spread of various diseases that can be prevented by vaccination, including hepatitis B, the Indonesian government has recently included the hepatitis B vaccination for toddlers in an immunization development program known as the Expanded Program on Immunization (EPI). Vaccination efforts have been able to reduce the number of people with the HBB and acute morbidity. Vaccination efforts have been able to reduce the number of people with HBV and acute morbidity.[6] However, vaccine effectiveness is affected by several host factors, including age, comorbidities, previous HBV exposure, time since vaccination, and other vaccine-related factors such as type, schedule, dose, and vaccine used.[7] In 2017, the percentage of pregnant women with reactive Hepatitis B surface antigen (HBsAg) in East Java, Indonesia, was 2.77%. It has been shown that vaccination against HBV infection in infants and neonates can reduce the burden of the disease. According to WHO, after completing the recommended immunization schedule, Hepatitis B vaccination should result in a level of antibody protection in 95% of individuals.[3-5]

Several related studies have shown that titers of Hepatitis B surface antibodies (anti-HBs) still provide a protective effect at 2-4 years, seven years, and even up to 12 years after primary vaccination.[8,9] Each individual's reaction to the hepatitis B vaccine's protective effect varies, and several factors, including age, male sex, obesity, chronic disease, genetic factors, alcohol use, and immunosuppressive conditions, affect how much seroprotection remains in those who have received the vaccine.[1] Several factors affect the protective effect of anti-HBs even though they have been vaccinated against hepatitis B, including non-compliance with cold chain vaccine storage procedures, wrong vaccination procedures, delays in giving vaccines at birth, loss of effectiveness of vaccines that are very susceptible during freezing and history of HBsAg-positive mothers.[10]

A meta-analysis of the factors of long-term protection following hepatitis B vaccination during infancy revealed that the mother's carrier status, the interval between the last two doses of the primary series, and the vaccine dose were the main determinants of antibody persistence. Lower vaccine doses given during infancy have also been associated with failure to respond to boosters.[11] Another meta-analysis assessing the immunogenicity of hepatitis B vaccine in premature and low birth weight infants found an association between preterm birth and a low immune response to hepatitis B vaccine.[12] Hepatitis B vaccine protection depends on immune memory rather than anti-HBs levels so that a booster dose is needed or not based on immune memory because anti-HBs levels can decrease over time.[13] It

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has been extensively studied in related fields how anti-HBs levels affect the status of long-term protection against hepatitis B vaccination. Several studies with cases and the use of the same method may produce different outcomes, therefore, we conducted a thorough meta-analysis on the factors that affect the long-term protection status of hepatitis B immunization by assessing anti-HBs levels in infancy to obtain new quantitative data.

MATERIAL AND METHODS

Search strategy

In finding all relevant publications regarding factors that influence the long-term protection status of hepatitis B immunization by assessing anti-HBs levels in infancy, we conducted a literature search through several secondary data sources obtained in the form of reputable national and international journal articles such as PubMed, ProQuest, Science Direct, and Web of Science from January 2000 to December 2021. Search for articles or journals using keywords and Boolean operators (AND / OR / NOT), which are used to expand or specify searches, making it easier to find the article or journal. The keywords in this study are adjusted to the Medical Subject Heading (MeSH). The search terms used are "immunity" OR "immune response" AND "hepatitis B antibodies" AND "hepatitis B vaccines" AND "infant" OR "newborn" OR "child". Figure 1 illustrates the flow chart of included studies. All observational studies were evaluated using the Newcastle-Ottawa Quality Assessment Scale (NOQS). Total NOQS scores were categorized into four study groups: very good (9-10 points), good (7-8 points), satisfied (5-6 points), and dissatisfied (0-4 points).[14]

Inclusion criteria

The included studies fulfilled the following criteria (1) observational studies related to factors affecting the long-term protection status of hepatitis B immunization in infancy; (2) studies with healthy children aged 5-18 years, regardless of previous immunization status, regardless of mother's hepatitis status; (3) the minimum number of research samples is more than 20 samples; (4) studies examining levels of anti-hepatitis B antibodies (anti-HBs). We also excluded the studies following (1) case report, review, editorial letter, opinion, randomized control trial, or systematic review; (2) studies that do not examine factors that influence hepatitis B immunization; (3) studies that did not examine anti-HBs antibody levels.

Data extraction and quality assessment

Several researchers independently chose and extracted the data, following guidelines. Data extraction is done using a data collector table. Author, year of publication, country, number of samples, age, gender, nutritional status, immunization frequency, vaccine dose, baseline characteristics, and anti-HBs titer were all recorded. A person under the age of 18 is considered a child for this study.[15] This meta-analysis study categorizes anti-HBs titer ≥10 mIU/mL as a protective against HBV infection.

In preparing this data, the researcher transfers important information from the selected literature into specified forms/tables to make it easier for researchers to identify the literature. A modified Cochrane data collection form was used.[16] This data collecting form comprises identities, characteristics, methods, and results from individual studies to help researchers examine the literature being reviewed, and it is then provided in tabular form to help researchers assess the characteristics of the research being reviewed.

Statistical analysis

We calculate the statistical combination of research results from two or more separate and similar studies, to explain research objectives such as calculating the treatment effect using the Odds Ratio (OR) or Relative Risk (RR) and confidence interval (CI) in each study. We also estimate the use of fixed effects models or random effects models, first calculating a Chi-square with a 50% limit, to assess heterogeneity. Then the overall effect size is also calculated as a summary of the results of the analysis and we also carry out a sensitivity analysis by eliminating journals and removing some low factors or evidence, then looking at the results of the sensitivity. With the Review Manager 5.4 program, data analysis is performed and results are calculated.

In this step of the meta-analysis, data on the number and proportion of variables that affect long-term protection status were summarized and compared using anti-HBs titer results. Subgroup analysis was also carried out in this study based on age, sex, gestational age, nutritional status, and hepatitis B immunization status in infancy. The meta-analysis results are explained in the form of forest plots and narratives to aid comprehension and offer readers with better conclusions on the research and synthesis of the articles analyzed.

RESULTS

There were 18 eligible studies with a total sample of 16,642 children involved in this study. Those studied were selected from screening related to the effect of age, sex, gestational age, nutritional status, and immunization status on levels of anti-HBs protection against hepatitis B immunization. There were 18 publications total, 15 cross-sectional studies, 2 cohort studies, and 1 case-control study. Table 1 summarizes the literature on factors that affect the long-term protective status of hepatitis B immunization in infancy. Using a random effect model analysis, Figure 2 illustrates the forest plot of age and gestational age factors on anti-HBs titers. Figure 2 shows the results of the data analysis of seven articles with mean child age <5 years, three articles reporting the effect of factor age >5 years compared to age <5 years on positive anti-HBs titers, and two articles examining gestational age <37 weeks against anti-HBs titers (OR 1.15, p= 0.08; OR 1.20, p<0.0001, and OR 2.5, p<0.0001, respectively).

Figure 3 shows the analysis of the sex factor on HBs titers. These findings indicate that the sex factor had no noticeable effect on the anti-HBs titer following infant hepatitis B vaccination. Figure 4 shows that the nutritional status of z scores for weight for age (WAZ) and length for age (LAZ) has a significant relationship with positive anti-HBs titers with p = 0.02 and p<0.00001. However, it is different with nutritional status z scores for weight for length (WLZ) and BMI for age, which do not show a significant relationship to anti-HBs titers.

Two articles provide the results of the influence of immunization status factors depending on the number of vaccine doses (4 doses versus 3 doses) on positive anti-HBs titers (seroprotection) (Figure 5). There is a significant relationship (p<0.00001) between the factor of immunization status and positive anti-HBs titers of hepatitis B immunization in infancy.

DISCUSSION

When conducting this meta-analysis, we found that age did not affect hepatitis B immunization anti-HBs titers. Sanou *et al.* (2018) showed results that children aged 1-5 years were more protected than other age groups.[31] Multivariate logistic analysis revealed that older age was a significant predictive variable for non-seroprotective levels, with adjusted ORs of 3.3, 9.1, and 14.2 among children aged 5 to <10 years, 10 to <15 years and ≥15 years compared to children aged <5 years where the value of p <0.01.[30] Another meta-analysis study revealed that the risk of an anti-HBs titer ≤10mIU/ml was reduced by 42% among subjects aged 10-20 years.[9] The influence of the age factor showed a weak, positive, linear correlation between age and anti-HBs titers. The highest anti-HBs antibody positive rate was in the age group under

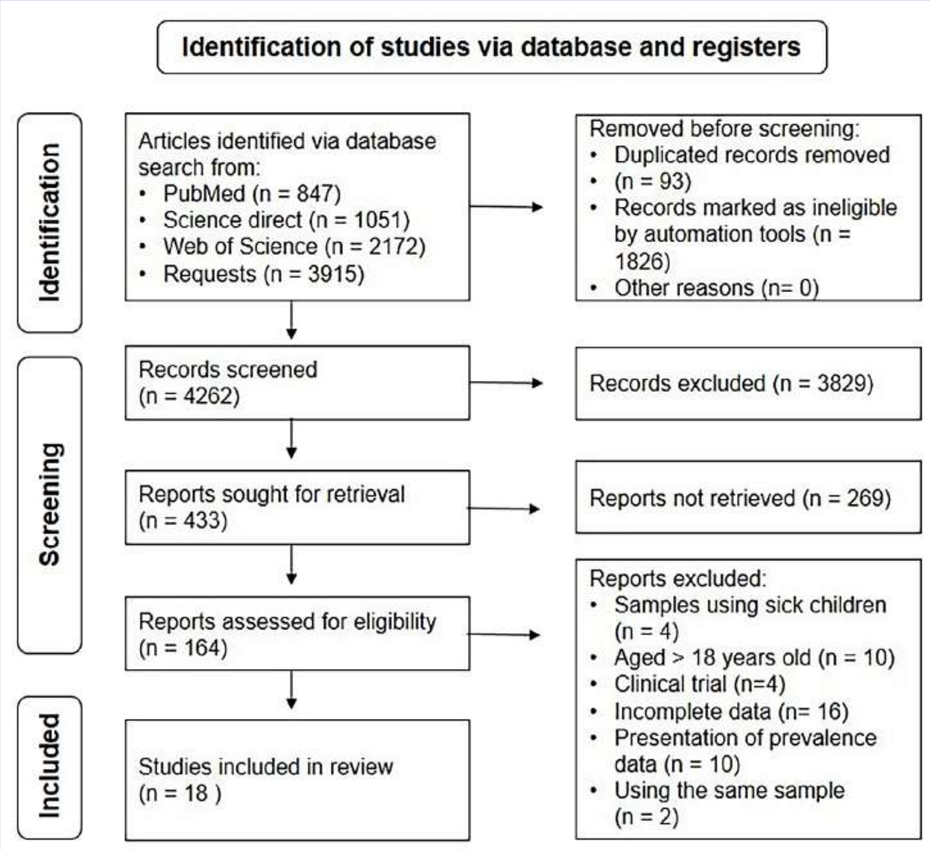

Figure 1: **Article screening flow based on preferred reporting items for systematic reviews and meta-analyses (PRISMA)**

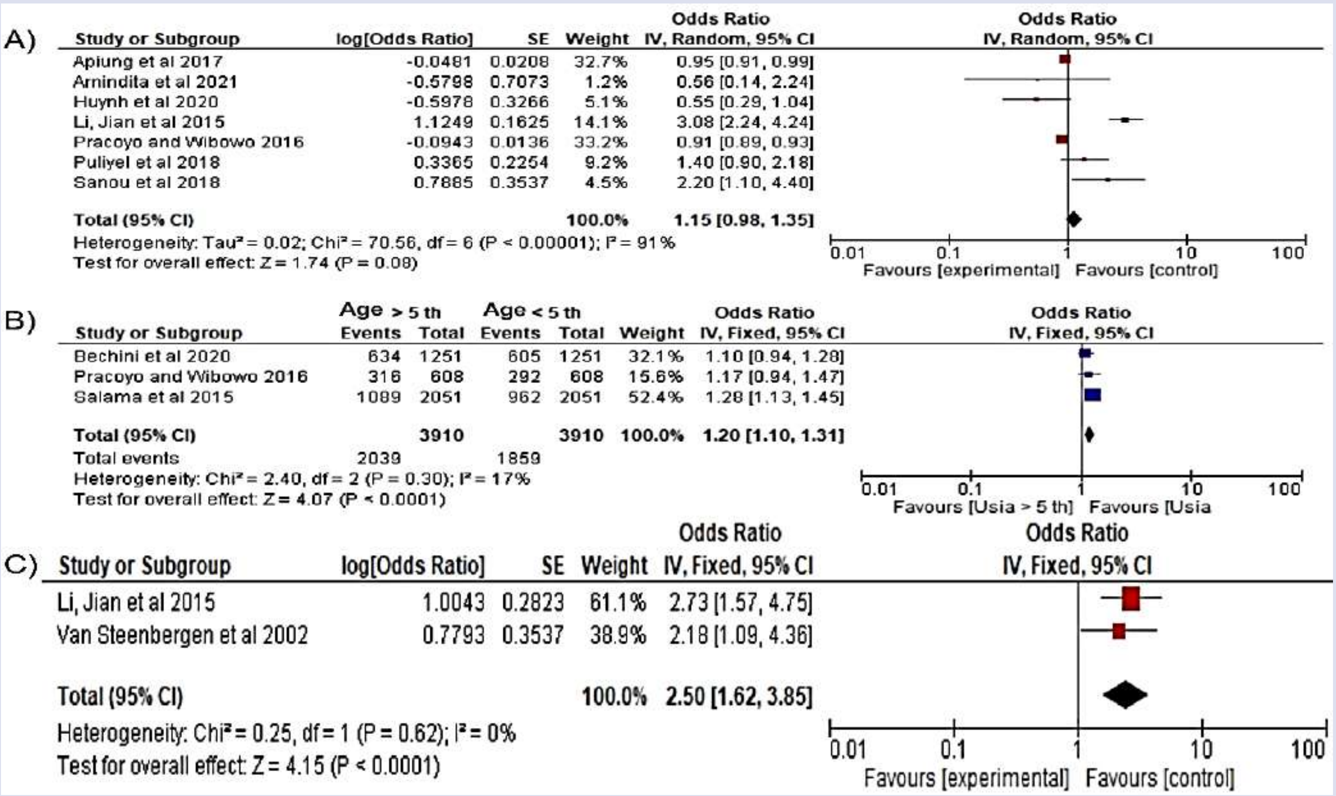

Figure 2: **Forest plot of the effect of age and gestational age on anti-HBs titers using a random effect model. A) The influence of the age of children less than 5 years on anti-HBs titers. B) Effect of age >5 years and age <5 years on positive anti-HBs titers. C) Effect of gestational age (<37 weeks vs >37 weeks) on anti-HBs titers**

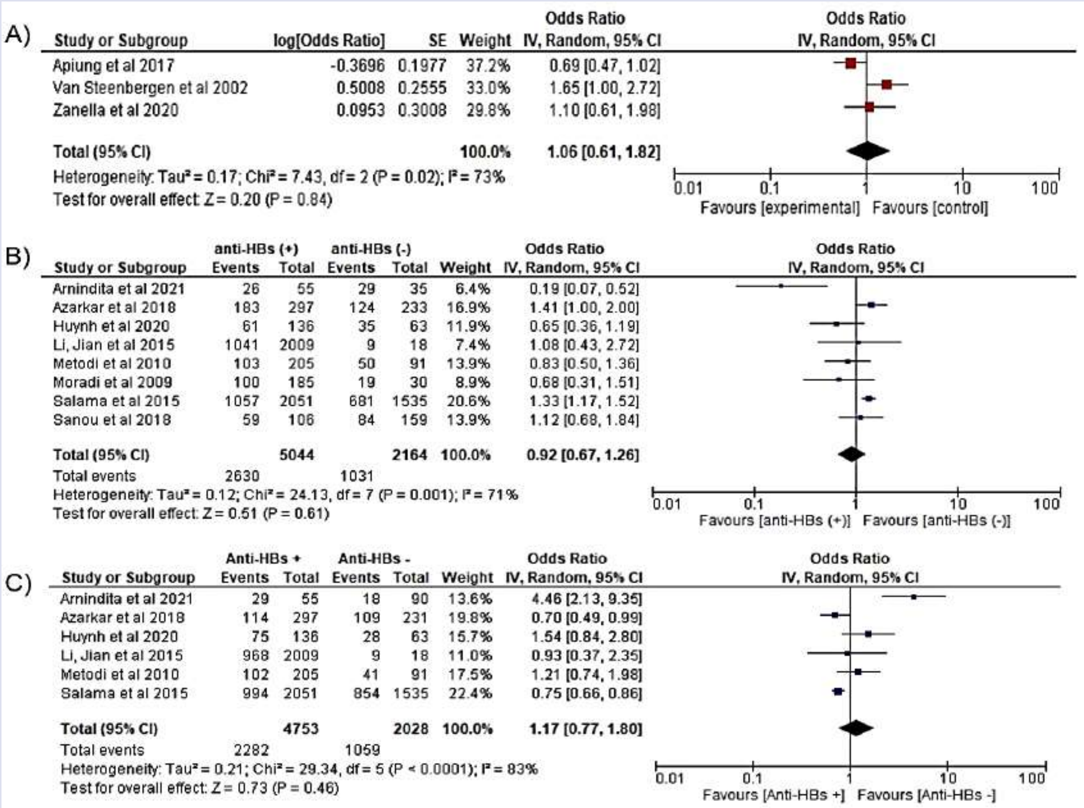

Figure 3: Forest plot of the effect of sex on anti-HBs titers using a random effect model. A) Three research articles on the effect of sex on anti-HBs titers. B) Effect of male sex on anti-HBs titers. C) Effect of female sex on anti-HBs titers

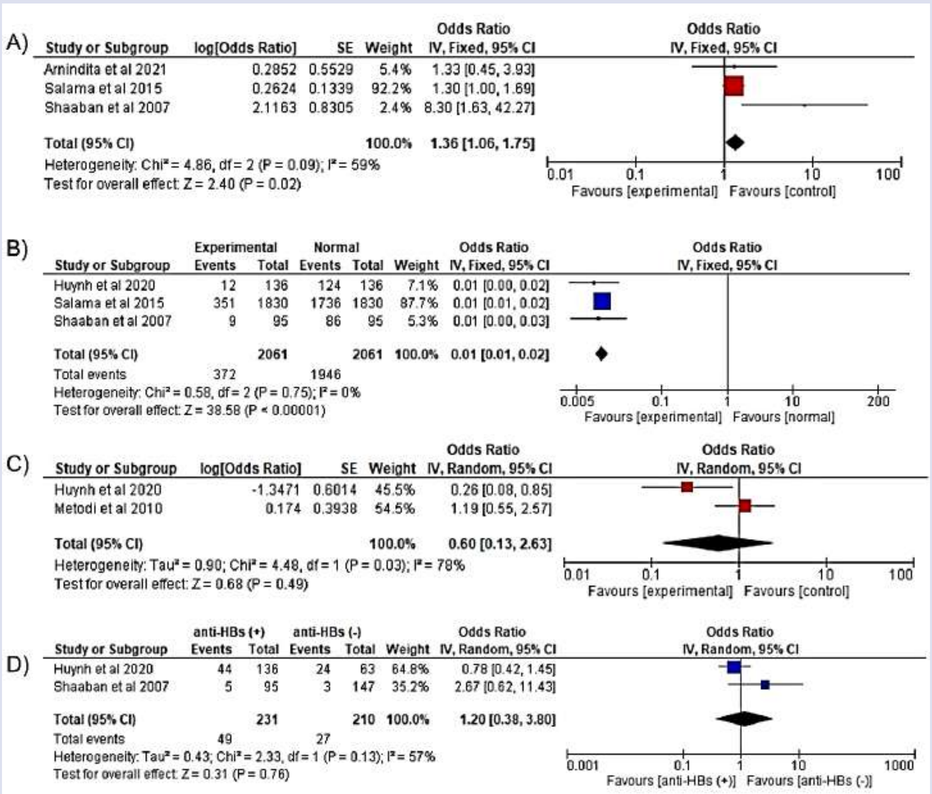

Figure 4: Forest plot of the effect of nutritional status on Anti-HB titers. A) Nutritional status based on weight for age against Anti-HBs titers. B) Nutritional status based on length for age against positive anti-HBs titers. C) Nutritional status based on weight for length against anti-HBs titers. D) Nutritional status based on Body Mass Index (BMI) for age against anti-HBs titers

Table 1: Sig literature characteristics of factors influencing long-term protection status of hepatitis B immunization in infancy.

No.	Authors(Year)	Study's design	Location	Number of samples	Age	Criteria for protective/ responsive Anti-HBs titers	♂: ♂ (%)	Nutritional status	Gestational age	Vaccine Frequency (doses)	NOQS scores	Study's results
1.	Accrombessi *et al.* (2020)[17]	*Cross sectional*	South Benin (West Africa)	140	9 months	*Responder*: 10-100 UI/L. *High responders:* ≥100 UI/L.	47/9:52.1	WAZ, LAZ, WLZ	< 37 weeks	3-4	NOQS 9 Selection 4 Comparability 2 Outcomes/Exposure 3	Four vaccine doses provide more protection against HBV infection than three doses (aOR; 95% CI: 2.49;1.03-6.03); p=0.04.
2.	Apiung *et al.* (2017)[18]	*Cross sectional*	Ghana (West Africa)	424	5-32 months 13.73 ± 5.72 months	≥10 mIU/mL	51 : 49	NA	NA	3	NOQS 8 Selection 3 Comparability 2 Outcomes/Exposure 3	The factor that has a significant effect on seropositivity is age (OR: 0.953; 95% CI: 0.915 – 0.993), sex (OR: 0.691; 95% CI: 0.469 – 1,020).
3.	Arnindita *et al.* (2021)[19]	*Cross sectional*	Surabaya (Indonesia)	90	1-<5 years a) 1- < 2 years b) 2- < 3 years c) 3- < 4 years d) 4- < 5 years	≥10 mIU/mL	52 : 48	WAZ	NA	3	NOQS 7 Selection 2 Comparability 2 Outcomes/Exposure 3	Factors related to anti-HBs (+): Age (3-<4 years), female sex, malnutrition (OR; 95% CI: 1.34;0.44-4.15, 1.12 (0.46-2.75, 1.96 (0.40-9.63).
4.	Azarkar *et al.* (2018)[20]	*Cross sectional*	Birjand (Iran)	530	6-18 years	>10 IU/L	58 : 42	NA	NA	3	NOQS 9 Selection 4 Comparability 2 Outcomes/Exposure 3	Sex (Female vs Male) no significant effect on anti-HBs <10 IU/L (OR; 95% CI: 0.71;0.501-1,003); p= 0.052.
5.	Bechini *et al.* (2020)[21]	*Cohort*	Tuscany (Italy)	2073	<18 years a) <1 years b) 1-4years c) 5-9 years d) 10-14 years e) 15-18 years	>10 mIU/mL	59.3 : 40.7	NA	NA	3	NOQS 8 Selection 4 Comparability 1 Outcomes/Exposure 3	Independent factor significantly associated with seronegativity was age 5-9 vs age 0-4 (aOR: 2.09; IK 95%: 1.69-2.57; p<0,001), age 10-18 vs age 0-4 (aOR: 2.69; 95% CI 1.94-3.72; p<0.001).
6.	Gomes *et al.* (2021)[22]	*Cross sectional*	Acre (Brazil)	522	2-5 years 4.3 ± 0.8 years	≥10 IU/L	49 : 51	NA	NA	4	NOQS 9 Selection 4 Comparability 2 Outcomes/Exposure 3	The logistic regression model associated with anti-HBs <10IU/L is age(OR: 0,63; 95% CI: 0.5-0.8) and sex (OR: 0.80; 95% CI: 0.55-1.18).
7.	Huynh *et al* (2020)[23]	*Cross sectional*	Ho Chi Minh City (Vietnam)	199	12-24 months a) <18 months b) ≥18months	≥10 mIU/mL	48 : 52	WAZ, LAZ, WLZ, andBMI	NA	3	NOQS 8 Selection 3 Comparability 2 Outcomes/Exposure 3	Factors related toanti-HBs (+): Age, sex, malnutrition (OR; 95% CI: 0.55; 0.29-1.03; 0.69; 0.37-1.30; 0.26; 0.08-0.88) (p=0.063; p=0.253; p=0.031).
8.	Li, Jian *etal* (2015)[24]	*Cross sectional*	Shanghai (China)	2,047	7-18 months a) 7-12 months b) 13-18 months	≥100 mIU/mL.*Low responder:*10-99 mIU/mL	52 : 48	NA	Premature, aterm	3	NOQS 9 Selection 4 Comparability 2 Outcomes/Exposure 3	Logistic regression investigation of variables of neonatal response to hepatitis B vaccination: 13-18 months of age (OR: 3.08; 95% CI: 2.24-4.22), male sex (OR: 1.39; 95% CI: 1.09-1.78), gestational age <37 weeks (OR: 2.73; 95% CI: 1.57-4.74).
9.	Magoni *et al.* (2009)[25]	*Cross sectional*	Grand Bassam (Ivory Coast)	1,038	12-59 months	>10 mIU/ml	12-23 months = 48.6 : 51.4 24-59 months = 50.6:49.4	NA	NA	0-4	NOQS 9 Selection 4 Comparability 2 Outcomes/Exposure 3	Multivariable logistic analysis: anti-HBs titer positively correlated with vaccination dose (OR= 2.2 for each dose).

No.	Authors(Year)	Study's design	Location	Number of samples	Age	Criteria for protective/ responsive Anti-HBs titers	♂: ♂ (%)	Nutritional status	Gestational age	Vaccine Frequency (doses)	NOQS scores	Study's results
10.	Metodi *et al.* (2010)[26]	*Cross sectional*	Dar es Salaam (Tanzania)	296	2- 59 months a) 2-12 months b) 13-24 months c) 25-36 months d) 37-48 months e) 49-59 months	≥10 mIU/mL	52 : 48	WLZ	NA	3	NOQS 8 Selection 3 Comparability 2 Outcomes/Exposure 3	Multivariate logistic regression analysis of factors associated with anti-HBs titers <10 mIU/mL: age 13-24 months, female sex, malnutrition and 3 doses of vaccine. (aOR; 95% CI: 0.56; 0.18-1.7; 1,17; 0.65-2.1; 1.19; 0.55-2.55; 0.07; 0.02-0.26).
11.	Moradi *etal.* (2009)[27]	*Cross sectional*	Golestan (Iran)	215	7-12 months	>10 IU/L	55 : 45	NA	NA	3	NOQS 7 Selection 2 Comparability 2 Outcomes/Exposure 3	HBV vaccine response was lower in males than in females (OR; 95% CI: 0.68; 0.28-1.61).
12.	Pracoyo and Wibowo(2016) [28]	*Cross sectional*	Indonesia	1,618	1-14 years a) 1-4 years b) 5-10 years c) 11-14 years	>10 mIU/mL	54 : 46	NA	NA	3	NOQS 9 Selection 5 Comparability 2 Outcomes/Exposure 2	The age factor (age group 1-4 years) is the most influential variable on anti-HBs titers (aOR; 95% CI: 0.91; 0.886-0.938); p<0.005.
13.	Puliyel *etal.* (2018)[29]	*Case control*	Delhi, Rajasthan, Uttar Pradesh, Uttarakhand, Gujarat (India)	2,671	1-5 years a) <1years b) 1-2years c) 2-3years d) 3-4 years e) >5 years	≥10 mIU/mL	62.6:37.4	NA	NA	4	NOQS 8 Selection 4 Comparability 1 Outcomes/Exposure 3	The level of HBsAb protection is significantly related to the increase in the number of vaccine doses (4 doses, OR; 95% CI: 228.4;120.8-431.9).
14.	Salama *et al.* (2015)[30]	*Cross sectional*	Egypt	3,586	9 months- 16 years a) <5 years b) 5- <10 years c) 10- <15 years d) ≥15years	≥10 IU/L	48.4:51.6	WAZ, LAZ or HAZ	NA	3	NOQS 9 Selection 4 Comparability 2 Outcomes/Exposure 3	Children with LAZ or HAZ and WAZ <Percentile 5 had significantly lower rates of non-protection; OR 1.3 (1.1-1.6) and 1.3 (1-1.7); p<0.05.
15.	Sanou *et al.* (2018)[31]	*Cross sectional*	BurkinaFaso (West Africa)	265	<10 years a) <1years b) 1-5 years c) >5years	≥10 mIU/mL	54 : 46	NA	NA	3	NOQS 9 Selection 4 Comparability 2 Outcomes/Exposure 3	Age 1-5 years is more protected than other age groups (OR = 2.2; 95% CI: 1.1-4.6; p=0.0065). No significant relationship was found between immune status and variables including sex. (OR = 1.1; 95% CI: 0.7-1.8; p=0.651).
16.	Shaaban *etal.* (2007)[32]	*Cross sectional*	Kairo (Egypt)	242	6-12 years	≥10 IU/L	48 : 52	WAZ, LAZ, andBMI	NA	3	NOQS 7 Selection 2 Comparability 2 Outcomes/Exposure 3	Multiple logistic analysis of significant risk factors related to anti-HBs titer <10 IU/L is age (aOR; 95% CI: 1.23; 1.04-1.5) and score WAZ >-2 SD(aOR; 95% CI: 8.3; 1.63-42.6).
17.	Van Steenbergen *et al.* (2001)[33]	*Cohort*	Amsterdam(the Netherlands)	521	7 months	≥100 IU/l. *Weak responder:* 10-100 IU/l	51 : 49	NA	<38 weeks 38–42 weeks >42 weeks	3	NOQS 7 Selection 4 Comparability 2 Outcomes/Exposure 1	Risk analysis of anti-HBs titers <100 IU/l (univariate and multivariate) is male sex OR (IK 95%)1.66 (1.03-2.70)/aOR (95% CI) 1.65 (1.00-2.73).
18.	Zanella *et al.* (2020)[34]	*Cross sectional*	Florence(Italy)	165	1-18 years	≥10 mIU/mL	53.3:46.7	NA	NA	3	NOQS 10 Selection 5 Comparability 2 Outcomes/Exposure 3	Male sex variable has no effect on anti-HBs titers (aOR; 1.10; 95% CI: 1.10; 0.61-1.98).

WAZ= z score for weight for age; LAZ= z score for length for age; HAZ= z score for height for age; WLZ= z score for weight for length; BMI= Body Mass Index; NA= Not available; OR= Odd ratio; CI= Confidence Interval; NOQS= Newcastle Ottawa Quality Assessment Scale.

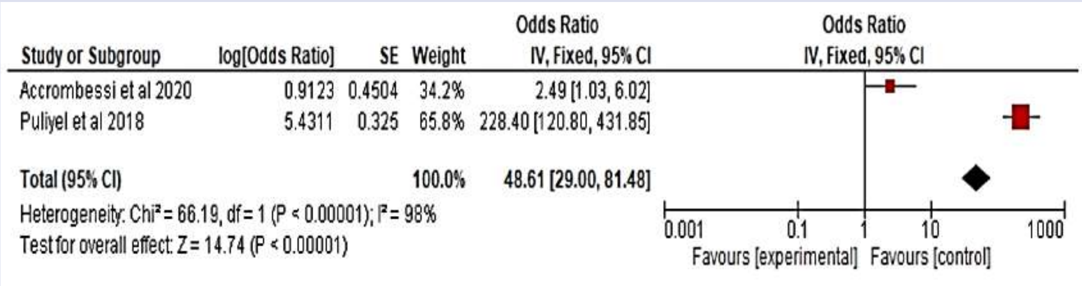

Figure 5: **Forest plot of the effect of immunization status on positive anti-HBs titers**

three years. The positivity rate decreased significantly after the age of seven. There was no statistically significant difference between the 8-11 year and 12-14 year age groups. The percentage of subjects with protective antibody levels increased statistically significantly in the age group >15 years.[35]

The seroconversion rate after primary HBV vaccination was ≥96% but protective anti-HBs titers were reported to decrease gradually over time. Several studies investigated long-term HBV immunity following primary vaccination. A decrease in antibody titers below 10mIU/mL does not always mean that there is no protection against the Hepatitis B virus. Anti-HBs antibodies are not the only marker of advanced immunity. Cellular immunity following HBV vaccination has been investigated in several studies. The presence of HBsAg-specific T cells in circulation after primary HBV vaccination indicates a specific immune response. Some vaccinated individuals who have lost antibodies have been found to contain HBsAg-specific memory T and B cells. Cellular immune memory provides a protective capacity against HBV that can continue even after the formation of anti-HBs antibodies following vaccination wears off.[9,35]

Our study found no effect of gender on hepatitis B immunization anti-HBs titers. Huynh *et al.* showed that the effect of sex on protective anti-HBs titers resulted in 136 (68.3%) infants had seroconversion positive HBsAb (≥10 mIU/mL), of whom 70 (51.5%) had HBsAb concentrations ≥100 mIU/mL and from the results of multivariate analysis showed no significant differences in sex.[23] The reasons why some infants do not respond well to primary vaccination against hepatitis B are complex. Hepatitis B dose, age, sex, prematurity, and the mother being positive for HBsAg and HBeAg were predictors of poor response. Sex is also a predictor of response and male infants are more likely to have an inferior response than female infants.[24,36] Various theories resulting from several studies found a decrease in the number of T lymphocytes in males compared to females, and men have lower serum IgM and IgG levels. The different immune response between male and female is also influenced by sex steroid hormones such as estrogen, progesterone, and testosterone, which are different in each sex. Moreover, there are many immunological genes that appear on the X chromosome, while only a few appear on the Y chromosome. Estrogen activates monocytes to secrete interleukin 10 (IL-10), which induces Immunoglobulin G (IgG) and Immunoglobulin M (IgM) secretion by B-cells, while testosterone impairs IgG and IgM production from B-lymphocytes, and inhibits interleukin 6 (IL-6) production from monocytes.[37,38]

Gestational age in this study showed a p value <0.0001 for anti-HBs titers, which means that a significant relationship was found. This result is in line with the study by Jiang *et al.* (2021) conducted on 1,849 children, 81 children with an adequate response (titers ≥100mIU/mL) and 21 inadequately responding children who were born prematurely showed that preterm birth was associated with an anti-HBs titer below 100 (mIU/mL).[39] The neonate's immune system is depending on gestational status and early exposure to a variety of stimuli, while preterm infants have a different immune system than full-term infants.

Premature infants have lower absolute numbers of lymphocytes, T cells, B cells, and T-helper cells, particularly between 6 and 9 weeks of age, when the first vaccine is given. However, it does illustrate that the premature infant's immune system quickly assembles and adapts after birth and follows stereotyped patterns early in life. In addition, perinatal conditions and postnatal exposure influence adaptive changes in the immune system of preterm infants. The first vaccinations given to infants at a certain age are important for antibody response, with older infants having higher antibody levels.[40]

Underweight or severely underweight children's nutritional status is assessed using the WHO z-score of weight for length/height for children under the age of five and the CDC table below the third percentile for children over the age of five, while obesity is assessed using the WHO z-score body mass index for age. Malnutrition is related to deficiency, excess, or imbalance of energy and other macro- and micronutrients.[41,42] In this study, we found that nutritional status based on WAZ and LAZ had a significant effect on anti-HBs titers having a p value <0.00001, but there was no effect on WLZ and BMI for age. The results of this study are inversely proportional to those conducted by Kasim *et al.* (2019), who found that there is no significant relationship between history of immunization and nutritional status based on WAZ (p= 1), LAZ (p= 0.638). Statistical results related to immunization history and nutritional status based on WLZ obtained p= 1, so there is no significant relationship between immunization history and nutritional status based on WLZ, which is in line with the results of this meta-analysis study.[43]

Maternal factors play a significant role in determining the nutritional status of children. Declining nutritional status in children can be caused by the emergence of infectious diseases in children, poor economic status, and poor parenting styles. Nutritional status has an important and complex impact on immune function because malnutrition can increase susceptibility to infection, and exacerbate it through nutritional loss. Severe malnutrition is associated with suppression of the adaptive immune response to routine vaccination against hepatitis B.[44] Malnourished children are more susceptible to infectious pathogens and more likely to die from infectious diseases. Malnutrition not only impacts growth but chronic malnutrition is strongly associated with lifelong cognitive delays.[45] However, despite the fact that many of these immunological changes appear to be synergistically influenced by malnutrition and infection, malnutrition can also be independently associated with changes in immune function.[46] Obesity has also been proven to be a predictor of impaired immunogenicity, as demonstrated by decreased antibody response to the hepatitis B, tetanus toxoid, rabies, and influenza vaccinations. These data shows that obesity correlates poorly with vaccine-induced immune responses in humans. Leptin resistance, which has been connected to obesity, is produced when a person's circulating leptin levels rise with aging and leptin signaling declines. Further research is required to fully understand the immunological pathways underlying obesity, as leptin resistance has been demonstrated to impact immune responses in obese individuals, particularly responses to influenza viruses.[47]

A significant relationship was discovered between the number of vaccine doses (complete vs. incomplete) and positive anti-HBs titers of hepatitis B vaccination in infancy in this study. Anti-HBs (protective antibody) titers show an increase with increasing dose of vaccination. Anti-HBs protective antibodies are present in approximately 70% of fully immunized children. Positive anti-HBs titers in unvaccinated infants may be due to active immunity developing in infants after infection. However, this rarely happens because most of these babies also have negative HBcAb. If this is active immunity after exposure to natural infection, the numbers tend to increase with age with more opportunities for exposure.[29] The meta-analysis report by Schönberger *et al*. (2013) assessed the determinants of long-term protection after hepatitis B vaccination during infancy. In that study it was concluded that lower vaccine doses given during infancy were associated with failure to respond to boosters.[11]

Our study should be evaluated in the following limitations. First, no contact was made with the researcher resulting in several articles that could not be analyzed because the data presented was inadequate for analysis. Second, only 18 publications that match the research topic were located since numerous journals did not offer comprehensive research data, including OR and CI values. While the strength of the relationship shown by each design differs, the research papers incorporated in this meta-analysis are research articles combined with an observational study design, which means that they can only describe association, not causality. Third, publication bias is a common problem, and may have occurred, especially in studies that are too long, where a few small studies show a dramatic effect. Fourth, studies used different diagnostic criteria for malnutrition, making it difficult to determine the degree of malnutrition and obesity in malnourished children as defined by current criteria. Nonetheless, we believe that this research is valuable and can serve as a foundation for future research.

CONCLUSION

In combination, this meta-analysis indicated that no significant effect of age and sex was found on anti-HBs titer in children who received hepatitis B immunization during infancy, although there is a significant effect between age <5 years vs >5 years on positive hepatitis B immunization anti-HBs titer. Then, a significant effect was found on gestational age <37 weeks, nutritional status based on weight for age, length for age, and immunization status based on the number of vaccine doses-- four and three doses respectively. In developing countries, it is important for health workers to periodically educate infants' parents regarding basic immunization for the prevention of Hepatitis B infection. To prevent preterm delivery and to give children the right nutrition based on their age and ability, enough and suitable nutrition for pregnant women must also be established. More research is required to evaluate the circumstances surrounding and other aspects of the condition of long-term protection from the hepatitis B vaccine in infancy, particularly utilizing a randomized control trial study design.

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CONFLICTS OF INTEREST

The authors declare there is no conflicts of interest.

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GRAPHICAL ABSTRACT

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