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A PROTECTIVE STATUS OF HbsAg AND Anti-HBs IN VACCINATED NEWBORNS FROM HEPATITIS B POSITIVED MOTHERS: A META ANALYSIS

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Abstract

Background: Mother-to-child transmission of hepatitis B virus makes a significant contribution to chronic hepatitis B virus infection. One strategy to prevent hepatitis B transmission from mother to child is by administering hepatitis B immunoglobulin (HBIg) and hepatitis B vaccination.

Methods: This meta-analysis used secondary data from articles taken from 2000 to 2020 through the PubMed database, Google Scholar. There were 5 articles for antiHbs and 4 articles for HBsAg that matched the inclusion and exclusion criteria. Analysis using the Revman Review Manager 5.4.

Results: The comparison of the proportion and confidence interval on HBsAg and anti-HBs status after hepatitis B vaccination in infants of HBsAg positive mothers showed that anti-HBs results with a combined effect magnitude of 0.89 (95% CI 0.83; 0.94), $p < 0.05$ while HBsAg status with a combined effect of 0.09 (95% CI 0.03; 0.015), $p < 0.05$.

Conclusion: The successful proportion of hepatitis B vaccination with HbIg is 89% and HbsAg positive status in infants is 9%.

Keywords: anti-HBs, HBsAg, hepatitis B, meta analysis

Introduction

Hepatitis B is a severe infectious disease and frequently infects the liver caused by the hepatitis B virus, which possibly causes chronic or acute illnesses. The Hepatitis B virus has infected about 2 billion people around the world until today. There are mostly 240 million of them who tend to become hepatitis B sufferers, and 360 million people are Hepatitis B surface antigen (HBsAg) carriers, and 220 million (78%) of these people are in Asia. Nearly 500 to 750 thousand forgotten people will die of hepatitis cirrhosis or develop liver cancer [3].

Hepatitis B has become an endemic disease in various countries in the world. Indonesia is a country with high endemicity of hepatitis B, the second-largest country in the Southeast Asian Region (SEAR) behind Myanmar. Riskesdas 2013 observed that the most common type of hepatitis infecting the Indonesian population is hepatitis B (21.8%) [5, 6]. Immunization is the most effective and safe strategy for controlling and eradicating hepatitis B virus infection. Based on Indonesia's 2012 health profile from the Ministry of Health of the Republic of Indonesia, Indonesia's hepatitis B immunization coverage ranks second lowest after the Philippines, at 73 percent [8].

The hepatitis B virus is commonly transmitted through the infected body liquids and blood exposure. Besides, mother-to-child transmission is the transmission central direction and contributes to chronic hepatitis B virus infection significantly. Approximately 3.9% of pregnant women are people with hepatitis with a risk of maternal transmission of nearly 90% of children who are vertically infected from mothers with positive HBsAg during 1st year-old of life will enhance chronic hepatitis B 90% growth, and will become carriers [10, 11]. One strategy to prevent hepatitis B mother-to-child transmission is by administering hepatitis B immunoglobulin (HBIg) immunization and hepatitis B vaccination [12]. Moreover, massive hepatitis B utilization is effective in decreasing the vertical transmission risk of hepatitis B [13]. The combined administration of hepatitis B and HBIG vaccines surprisingly proved to be more significant in reducing the vertical transmission of hepatitis B. Previous studies have reported that HBIG administration and hepatitis B vaccine in 24 hours of birth has a preventive effect around 85-95% [14]. Although vaccination is mandatory in many countries, the Centers for

Disease Control and Prevention (CDC) and Indonesia do not apply the mandatory post-immunization antibody response examination in infants. There is a possibility of no antibody formation after the complete administration of the vaccine (non-responder). This indicates that screening or revaccination is needed, especially in at-risk groups [15]. Further analysis is necessary on the protection benefits of immunization.

Meta-analysis is an integrated procedure of several studies. In the pyramid of evidence-based medicine, ranked by freedom from research bias, meta-analyses top the list [16, 17]. focusing on the same question, which aims to produce a quantitative estimate of the phenomenon under study [18, 19]. Meta-analysis contributes to education to better collect scientific evidence, disseminated across studies applying the same 261 science required from mainstream research [20]. Hence, we conducted a meta-analysis to evaluate the results consistency of studies that have been carried out regarding HBsAg protection status and anti-HBs levels with a history of HBIG and hepatitis B immunization born to HBsAg-positive mothers.

Methods

Eligibility criteria

This study used a quantitative method with a meta-analysis approach based on PRISMA guidelines (Figure 1). The journal understudy has been published within the years 2000-2020. The HBsAg and Anti-HBsAg status after hepatitis B vaccination in infants to hepatitis B positive mothers had a systematic deeply investigated literature search. The subjects of the study we were looking for were pediatric patients up to the age of 18 years, the articles studied were prospective cohorts or retrospective cohorts, and the articles were obtained in full-text form and had been reviewed. Excluded research journals include case study articles or case series, subject study designs in the form of experimental animals, non-published articles, incomplete journal data, journals that are not open access, and journals in the form of abstracts. The collected data is managed based on the preferred reporting items for systematic review and meta-analysis (PRISMA). All articles collected are identified, screened, eligible, and include to determine the articles to be analyzed. In assessing the quality of research and journal feasibility, there are several criteria used to evaluate the research results and the journals used.

Literature search

Search literature through free search or electronic databases. The electronic database in this research literature search used PubMed and Google Scholar to identify relevant research. In this step, searching for keywords (search terms) using Boolean Operators (Search Commands) includes: AND / OR / NOT. The search terms used were vaccine|| AND Hepatitis B|| AND (Newborn OR Infant OR Baby OR Babies) AND (—high risk|| OR Hepatitis B Mother||).

Literature quality assessment

In this present study, the preferred reporting items for systematic review and meta-analysis (PRISMA) is the method that is responsible to accumulate all data searches. All articles collected are identified, screened, eligible, and include to determine the articles to be analyzed. In assessing the quality of research and journal feasibility, some criteria applied to evaluate the research results and the journals used. The checklist of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) was used to analyze the research of methodological quality. This instrument was used to evaluate the communication clarity of research results in observational research and has been utilized in a current systematic review to assess the methodological quality of observational studies. Around 9 related to the methods section were qualified out of the 22 checklist items, which assessed various methodological aspects of observational research. The quality of research methods is listed as follows: articles that meet 0–3 out of 9 items are considered to have low methodological quality, 4-6 items as medium methodological quality, and 7-9 items as the highest methodological quality.

Data Extraction

In this data preparation, important information is transferred from the selected literature into certain forms/tables to make it easier for researchers to identify the literature. In this study, a modified collected data form from Cochrane (The Cochrane Library) was used. This data contains the identity, characteristics, methods, and results of the research specifically to make it easier for researchers to analyze the literature reviewed and then presented in tabular form to make it easier for researchers to analyze the characteristics of the research being reviewed.

Statistical analysis

The data that has been collected is analyzed using meta-analysis, which is a combination of statistical research results from two or more separate and similar studies, to answer research questions. The Meta-Analysis process includes: 1) Calculating the treatment effect (using the mean difference) and confidence interval in each study; 2) Calculate the overall treatment effect as a summary of the results of the analysis. The Meta-Analysis process is carried out using the Revman Review Manager 5.3 software [21, 22]. The results of the meta-analysis are described and explained in the form of forest plots and narratives to facilitate understanding and provide clearer conclusions to readers on the results of the research and synthesis of the articles reviewed, and funnel plots to see any publication bias.

Results

In this study, the analyzed studies consisted of external sources through the PubMed and Google Scholar databases with the keywords "vaccine" AND "Hepatitis B" AND " (Newborn OR Infant OR Baby OR Babies) AND ("high risk" OR "Hepatitis B Mother". ") as shown in Figure 1. Of the 312 articles that were originally identified in the literature search, journals in foreign languages were also found, the study was duplicated so that 25 articles met the inclusion criteria: 25 articles on HBsAg status of infants born hepatitis B post-vaccination to hepatitis B positive mothers. There are 15 full-text articles can be accessed, and 5 articles that meet the quality and quantity screening criteria. The determination of the selected research criteria is based on the availability of data and the validity of the measurement method. Exposure was measured by looking at HBsAg status and post-vaccination anti-HBs levels. All studies included in the review as having high methodological quality were assessed against the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (Table 1).

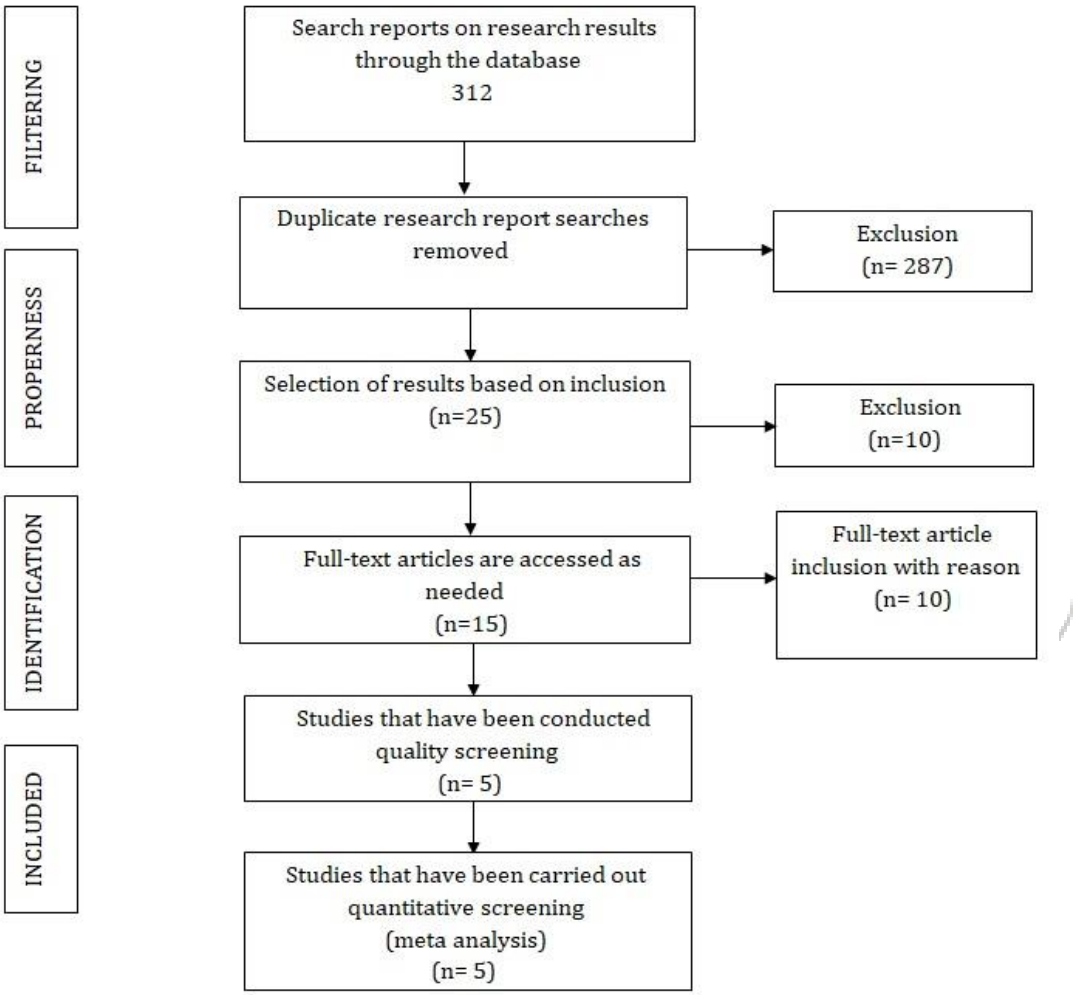


Figure 1. PRISMA prism flow chart results.

The five studies obtained have gone through a quality assessment process with a cohort study design, with settings in Asia represented by China, Europe, namely Italy, and America. Participants in the journals that were analyzed were all pairs of mothers and babies born to mothers with positive HBsAg. As for the confounding factors such as the presence of maternal Hbv DNA, maternal HbIg, and HBeAg, forest plot analysis will be carried out to combine the varied data, and publication bias analysis will be carried out by performing the Begg and Egger analysis. Of the five journals obtained, five of them have gone through the STROBE checklist stage and meet the requirements with a total score of 9.

Table 1. Article quality rating.

Study case	Study Design	Setting	Participant	Variable	Data Source/Measurement	Bias	Study Size	Quantitative Variable	Statistic Method	Value	Reference
Yonghao et al, 2017	+	+	+	+	+	+	+	+	+	9	[1]
Ko et al, 2014	+	+	+	+	+	+	+	+	+	9	[2]
Mele et al, 2001	+	+	+	+	+	+	+	+	+	9	[4]
Zhang et al, 2004	+	+	+	+	+	+	+	+	+	9	[7]
Gong and Liu 2018	+	+	+	+	+	+	+	+	+	9	[9]

Data extraction was implemented using a modified data collection form from Cochrane. The data that the researcher collected from the articles included: the author, the title of the article, the place of study, the research sample, the study design, the proportion of anti-HBsAg and HBsAg post-vaccination (Table 2). The systematic review study involved 5 studies with a total of 10,949 subjects. There were 4 out of 5 studies that reported infant HBsAg status, and 3 out of 5 studies reported maternal HBeAg condition. The meta-analysis stage was carried out by summarizing and comparing the proportion of Anti-HBs situation with infants born hepatitis B post-vaccination to hepatitis B positive mothers.

Table 2. Anti-HBs post-vaccination characteristics.

No.	Title/Journal Number	Author, Year, Country, Journal	Total Sample	Research Method	Exposure assessment / instrument	Confounding factor	Result
1	PMID: **28199772** DOI: 10.1111/jvh.12694	Yonghao et al, 2017 China J Viral Hepat	451 maternal-infant	Retrospective cohort	Anti-HBs post-vaccination checks	At the time of administration of the vaccine, HBeAg positive material who did not get HbIg within pregnancy	90.4% (396/438) indicated a positive response to HepB vaccination with an anti-Hbs level 10 mIU/mL. 5.3% (23/438) babies have positive HBsAg
2	PMID: **24560676** DOI: 10.1016/j.vaccine.2014.01.099	Ko et al, 2014 USA Vaccine	8654 maternal-infant	Retrospective cohort	Anti-HBs post-vaccination checks	Maternal HBeAg status, viral load, gestational age, birth weight, fourth vaccine dose, the timing of HbIg administration, time of administration of a vaccine after birth, post-vaccination serology	94.7% of infants responded to primary hepatitis B administration. There is no data regarding the incidence of positive HBsAg
3	PMID: 11509998 DOI : 10.1086/323396	Mele et al, 2001 Italy J Infect Dis	552 maternal-infant	Retrospective cohort	Anti-HBs post-vaccination checks	Not evaluated	400 (79.2%) of 505 consistently possessed a protective anti-HBsAg titer ≥10 mIU/mL. A total of 3/552 HBsAg (+) patients
4	PMID: 2524075 DOI: 10.1016/j.vaccine.2014.08.078	Zhang et al, 2014 China Vaccine	1202 maternal-infant	Retrospective cohort	Anti-HBs pos vaccination checks	Maternal HBeAg level, Maternal anti-HBs titer	40/1202 babies were found to be HBsAg positive. Infants anti-HBs positivity rates with maternal anti-Hbs titers <10 IU/L, 10-500 IU/L and ≥500 IU/L were 90.3% (168/186), 90.5% (219/242) and 80.2% (89/111) respectively, p = 0.011.

5	PMID: 29399100 doi: 10.3892/etm.2017.5474	Gong and Liu 2018 China Exp Ther Med.	90 maternal-infant	Retrospective cohort	Anti-HBs post-vaccination checks	HbeAg level	82/90 had anti-HBsAg post-vaccination (91%) and 5/90 babies had HBsAg (+)

There are exactly 5 journals are reporting the results of Anti-HBs status of infants born HbIg post-vaccination to hepatitis B positive mothers with a combined effect magnitude of 0.89 (95% CI 0.89; 0.94), p= <0.05. This study is heterogeneous because it can be seen in the results of the χ^2 heterogeneity of 52.45%, so a random-effects model is used to combine the results (Figure 2). Figure 3 shows that 4 journals are reporting the results of HBsAg status after infants born hepatitis B vaccination to hepatitis B positive mothers with a combined effect magnitude of 0.09 (95% CI 0.03; 0.15), p= <0.05. This study includes heterogeneity because it can be seen in the results of the Chi2 heterogeneity of 80.39%, so a random-effects model is used to results incorporation (Figure 3). In the funnel plot analysis that assessed the proportion of HBsAg and anti-HBs using the Begg's and Egger's test, no publication bias was found with p=0.4969 and p=0.2529; p=0.6242 and p=0.1937 respectively (p>0.05) as shown in Figure 4 and 5.

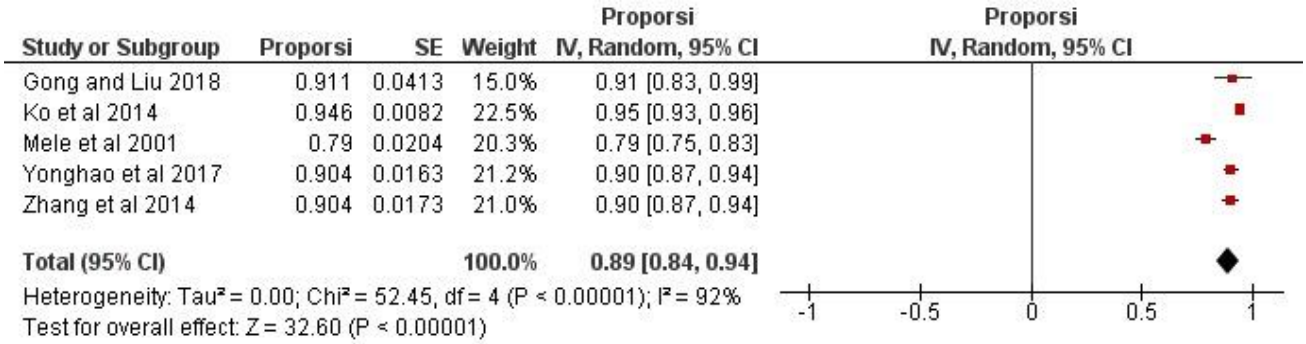


Figure 2. The results of the forest plot of the proportion of anti-HBs status of infants born HbIg post-vaccination to hepatitis B positive mothers.

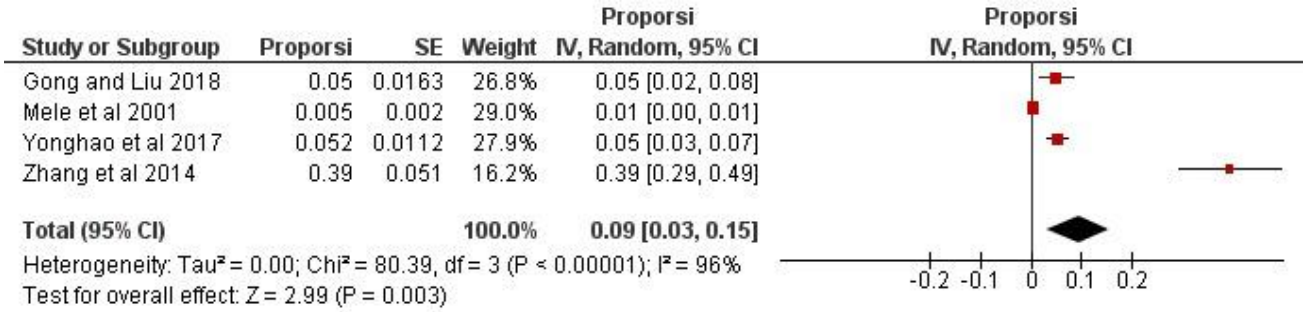


Figure 3. The results of the forest plot of the proportion of HBsAg status of infants born hepatitis B post-vaccinationto hepatitis B positive mothers.

Discussion

The systematic study of subjects involved 5 studies with a sum of 10,949 subjects. There were 4 out of 5 studies that reported infant HBsAg status and 3 out of 5 studies reported maternal HBeAg status. Five journals report the results of Anti-HBs status of infants hepatitis B post-vaccination from hepatitis B positive mothers with a combined effect magnitude of 0.89 (95% CI 0.89; 0.94), p=<0.05 while for HBsAg status obtained from 4 journals that reported the results of HBsAg status of infants born hepatitis B post-vaccination to hepatitis B positive mothers with a combined effect magnitude of 0.09 (95% CI 0.03; 0.15), p <0.05. This shows that the proportion of successful hepatitis B vaccination with HbIg is 89%, and HBsAg positive status in infants is 9%.

Mother-to-Child Transmission (MTCT) prevention of hepatitis B virus is referred to as its mechanism. This strategy includes care for mothers within pregnancy, efforts for giving birth and their newborn post-treatment. The study found that rates of non- and hypo-response to hepatitis B vaccine were higher in infants born to HBsAg positive mothers than in newborns born to normal mothers in the general population. These babies are at a higher risk of being carriers of the hepatitis B virus. Hepatitis B immunoglobulin belongs to the category of passive antibodies. Hepatitis B immunoglobulin can produce anti-HBs antibodies within hours of injection. Hepatitis B immunoglobulin is a passive immunization for patients who have been exposed to the hepatitis B virus. Some studies showed the two immunizations combination above has certain advantages in

blocking the transmission of the hepatitis B virus from mother to baby. The probability of infants born hepatitis B carrier to HBsAg positive mothers can be reduced by approximately 90% with appropriate vaccine and HbIg administration [23].

Research conducted by Yong Hao et al. (2017) with 438 infants of HBsAg positive mothers who were given three doses of hepatitis B vaccination. Based on vaccine results, it was found that approximately 91.8% (402/438) infants completed all three doses of Hepatitis B vaccine immediately, while 36 infants delayed at least one dose. All 438 infants tested for anti-HBs and HBsAg found 90.4% (396/438) to respond positively to Hepatitis B vaccination with anti-HBs levels of 10 mIU/mL. The mean geometric titer (GMT) of anti-HBs in infants decreases gradually at 1–2 months. This value continued to decrease dramatically at 7–8 months after the completion of three doses of the Hepatitis B vaccine. The ratio of anti-HBs positivity decreased dramatically at 11–12 months after three doses of the Hepatitis B vaccine administration [1].

Ko et al. evaluated vaccine response in neonates and found that 8199 (94.7%) of 8654 infants showed a vaccine response after completing the initial 3 or 4 dose HepB series. From the analysis, 1407 (16.3%) infants received four doses of the vaccine. The fourth with vaccine dose-response ($p<0.01$). There are 210 infants completed the second vaccination at the analysis time from 455 non-responders. 199 (94.8%) of them showed a response after the second vaccine with a created 97.0% responses [2].

Mele et al. directed research on evaluating the effectiveness of hepatitis B vaccination in HBsAg-positive mothers in Italy. This study surveyed 522 infants born to HBsAg positive mothers in a range of 1985 to 1994 and assessed the protection supplied by anti-hepatitis B virus (HBV) immunization at birth. Infants are treated hepatitis B immunoglobulin and hepatitis B vaccine at birth. At 5-14 years post-immunization, 17 adolescents (3.3%) were positive for anti-Hb core antigen, and three children were HBsAg positive specifically. One carrier adolescent had a double mutation, with prolinerserine substitution at codons 120 (P120S) and 127 (P127S) in the HBsAg determinant. From 522 adolescents , 400 (79.2%) of 505 consistently give a protective anti-HBsAg titer of 10 mIU/mL. Therefore, infants born HBV vaccination to HBsAg-positive mothers is impressively efficient and long-term immunity affordable [4].

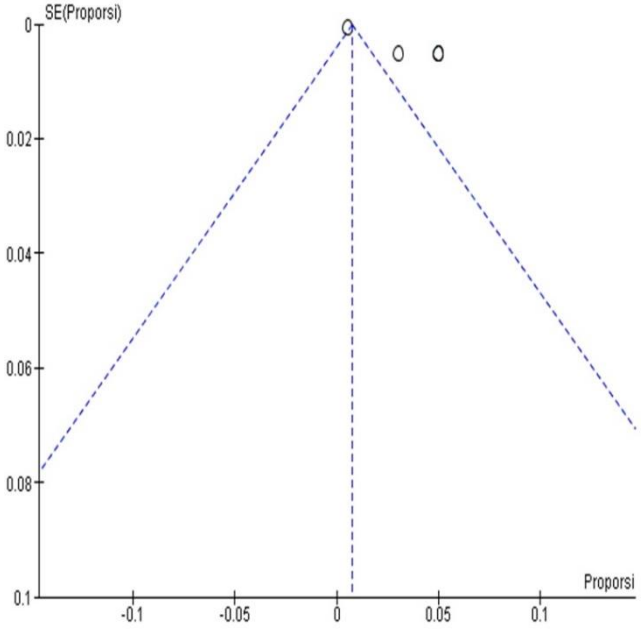
The meta-analysis by Chen et al. in 2020 evaluated both hepatitis B immunoglobulin advantages and dangers and hepatitis B vaccine in limiting mother-to-child transmission in HBsAg positive pregnant women during the antenatal period. Sixteen randomized controlled trials involving 2440 pregnant women who were HBsAg positive were included in the meta-analysis. Compared with the placebo group, the HbIg and hepatitis B vaccine group had a sufficient reduction of HBsAg positive newborns number (relative risk [RR]: 0.2, 95% confidence interval [CI] [0.18, 0.40]). , $p<0.00001$), HBV-DNA positive (RR: 0.25, 95% CI [0.09, 0.71], $p=0.010$), and showed dramatically increase of infants born number with positive anti-HBs (RR: 3.95). , 95% CI [3.11, 5.00], $p<0.00001$). After a year of follow-up, the number of HBsAg-positive newborns decline continously (RR: 0.09, 95% CI [0.04, 0.20], $p<0.0001$), and the number of newborns with anti-HBs positivity persistently increased in the HbIg and hepatitis B vaccine groups (RR: 1.30, 95% CI [1.22, 1.38], $p<0.00001$). Compared with the HbIg group, the HbIg group and hepatitis B vaccine had no notable change in HBsAg positive newborns (RR: 1.68, 95% CI [0.66, 4.30], $p=.28$), and marked notable reducing number of HBsAg positive newborns (RR: 0.31, 95% CI [0.12, 0.84], $p=0.02$). Therefore, hepatitis B immunoglobulin and Hepatitis B vaccine can be an alternative way for pregnant women who are HBsAg positive to prevent mother-to-child transmission [24].

Some aspects that affect the efficacy of giving hepatitis B and HbIg vaccines to neonates, including maternal HBeAg status. Immunoprophylaxis failure was reported to be higher in the single administration of Hepatitis B vaccine without HbIg in this group. Zhang et al. reported that there were no neonates infected with hepatitis B virus in the maternal HBeAg negative group regardless of HbIg status [7, 25].

Without prophylaxis, the risk of vertical transmission of the hepatitis B virus is high. The risk is highest for HBsAg-negative and HBeAg-positive mothers (transmission rate: 70%-90%), and low for HBsAg-positive HBeAg-negative mothers (transmission rate: 10%-40%). Active hepatitis B vaccination is highly effective in inculating infants, but in newborns to HBsAg-positive mothers, immunoglobulins are also required to protect against vertical transmission. HBsAg positive women can contribute to new cases of HBsAg positive newborns, who are more likely to develop carriers and chronic disease [26]. As noted earlier, high levels of HBV DNA and HBeAg positive status in pregnant women are considered the most important risk factors for hepatitis B virus MTCT. The rate of hepatitis B transmission in infants born to HBeAg positive mothers has decreased from >90% to about 3-7% with a combination of the HbIg vaccine and hepatitis B virus. However, other studies have shown that the failure rate of immunoprophylaxis in newborns born to mothers with HBeAg positive and hepatitis B virus is high, reaching 8-32% [27].

Immunoprophylaxis is given to newborns clearly reduces the hepatitis B virus transmission incidence in the perinatal period. With universal infant vaccination, the incidence of HBsAg decreased from 9-12% to <1% in China. Many studies including the Cochrane systematic review have shown that vaccination alone is not sufficient to prevent MTCT of hepatitis B virus in these HBsAg positive mothers, while the combination of Hepatitis B vaccine with HbIg is more efficient in reducing MTCT prevalence than vaccine or HbIg alone. The WHO guidelines also state that HbIg concomitant vaccination may provide additional benefits for infants of HBsAg-positive mothers, especially if they are HBeAg-positive. Transmission rates of hepatitis B virus have been decreased by 85-95% by universally active and passive immunoprophylaxis of newborns [28, 29].

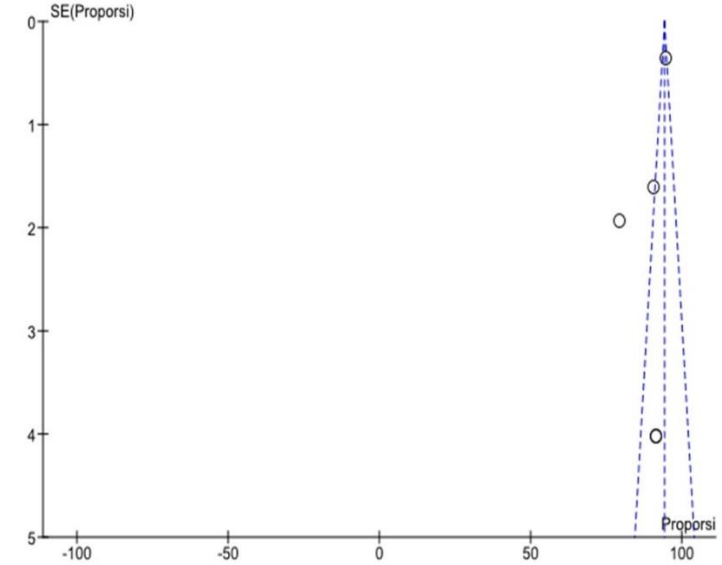
In this present study, the characteristics of the literature based on the type of research were 5 studies that looked at the proportion of HBsAg and Anti-HBsAg after vaccination. All studies included in this meta-analysis had high methodological quality referring to the procedure referred to the study method (STROBE). All studies have appropriate designs and methods to achieve the research objectives and investigate confounding to avoid any bias which would affect the results (Figure 4 and 5). For this reason, we believe that the results obtained in this study are reliable.



Publication bias

Egger's test	
Intercept	11.6608
95% CI	-19.9087 to 43.2303
Significance level	P = 0.2529
Begg's test	
Kendall's Tau	0.3333
Significance level	P = 0.4969

Figure 4. The results of the funnel plot of the proportion of HBsAg.



Publication bias

Egger's test	
Intercept	-5.8379
95% CI	-16.9678 to 5.2920
Significance level	P = 0.1937
Begg's test	
Kendall's Tau	0.2000
Significance level	P = 0.6242

Figure 5. The funnel plot results of the proportion of Anti-HBs.

Several limitations cannot be avoided, namely the existence of measurements at various times, the administration of HbIg, the characteristics of the material standards used are quite diverse, and some journals do not include complete research results, namely the confidence interval value. In this meta-analysis of all journals, the study design was a cohort.

Conclusion

In summary, the proportion of successful HBsAg vaccination with HbIg was 89% and HBsAg positive status in infants was 9%. HBeAg status affects the success of vaccination. Health services are expected to continue to broadcast maternal HBeAg status, provide vaccinations and HbIg according to the recommended schedule.

Acknowledgment

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Conflict of Interest

There are no conflict of interest in this present study.

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