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Immune response to hepatitis B vaccine in children born to HBsAg positive mothers: a meta-regression analysis

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Summary

Purpose: Mother-to-child transmission (MTCT) is the main mode of spread of hepatitis B virus (HBV), worldwide. The authors performed a meta-analysis to compare the effects of three measures for prevention of MTCT. *Materials and Methods:* Medline (PubMed) was searched and experts were contacted for references. Odds ratio (OD) and 95% confidence intervals (CI) were used as measures of effect sizes. *Results:* A meta-analysis was performed on randomized controlled trials and non-randomized studies comparing the index of MTCT among five groups of pregnant women. Among infants born to HBsAg-positive mothers, there were no significant differences in anti-HBs positive rates between the vaccine-only group and combined-immunization group by age 8-12 months. In infants aged 7-15 months and infants aged 16–24 months, anti-HBs positive rate was 92.6% and 84.0% respectively. Immunoprophylaxis failure rate in mother's age < 28 group was significantly higher than that of ≥ 28 group, and that in vaccine-only group was significantly higher than vaccine plus HBIG group. *Conclusions:* HBIG and HB vaccine as an immune prophylaxis in infants born to HBV carrier mothers, beginning after birth, is effective in preventing MTCT of HBV.

Key words: HBV; Mother-to-child transmission (MTCT); Hepatitis B immunoglobulin (HBIG); HB vaccine.

Introduction

Hepatitis B virus (HBV) causes inflammation of the liver in humans and is a major public health problem worldwide. About a quarter of the world population (> 2 billion) has been infected with HBV, including 350 million with chronic or lifelong HBV infection [1]. Now, mother-to-child transmission (MTCT) is the major route for HBV transmission and subsequent chronicity, accounting for 40–50% of HBV carriers [2, 3]. In the past, because of lack of intervention, infants born to mothers-HBsAg positive but HBeAg negative-have about 40% chance of acquiring perinatal HBV infection. On the other hand, the incidence of perinatal infection is even greater, around 70–90%, when the mother is both HBsAg and HBeAg positive [4, 5].

Using hepatitis B vaccine (HB vaccine) alone can prevent at least 75% of infants who are born to HBeAg and HBsAg both positive mothers developing persistent carrier states. Meanwhile, the use of hepatitis B immune globulin (HBIG) and vaccine in such infants appears to increase the latter to as high as 95% [6, 7]. Obviously, the combined use of drugs can significantly reduce the incidence of MTCT. However, MTCT of HBV still occurs despite the adequate administration of HBIG and HB vaccine at birth. The immunoprophylaxis failure rate was 3.4 % among infants of HBsAg-carrier mothers, and the HBV breakthrough infants were all from HBeAg-positive mother among whom the failure rate was 9.4% [3, 8].

HBsAg positive but HBeAg negative and HBsAg and HBeAg both positive are at increased risk of contracting MTCT, and their children show lower antibody response to hepatitis B vaccination compared to the general population, even though a lack of, or a low response to vaccination is reported to occur in 4% to 10% of healthy subjects [9]. This systematic review and meta-analysis aimed to estimate seroprotection rates and identify host or vaccine factors associated with varying immune response following hepatitis B vaccination in infants of HBsAg-carrier mothers.

Materials and Methods

Medline/PubMed, Embase, the Cochrane databases, and Web of Knowledge were searched for all relevant cohort studies. Only English language literature was included. The search was designed using the key words "mother-to-child transmission (MTCT)" or "mother-to-infant transmission (MTIT)" or "vertical transmission" or "perinatal transmission", "hepatitis B virus" or "HBV", and "HBsAb" or "anti HBs" or "Hepatitis B surface antigen antibody" or "anti-hepatitis B surface antigen". The authors included all randomized controlled trials, cohort trials, and prospective, controlled, and non-randomized trials. They also performed a full manual search of the bibliographies of selected studies to identify additional studies. To maximize data acquisition, they contacted authors whose articles contained insufficient information.

After removal of duplicate publications, the titles and abstracts of the remaining articles were screened for relevance to the topic. Recorded variables included the seroprotection rate, time from last vaccine dose to seroprotection, and other covariates such as vaccine dose, schedule and brand, site and route of vaccine ad-

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Table 1. — *Patient characteristics: demographics and serological profiles of study participants. The accelerated vaccine schedule was a rapid two-month schedule (0, 1, and 2 months), and the standard schedule was a six-month schedule (0, 1, and 6 months).*

Items	n	Anti HBs (+) infants n (%)	Logistic regression analysis	
			RR	*p* value
Mother's age				
< 28 years	793	731 (92.18)	0.108	<0.001
≥ 28 years	1,222	1,185 (96.97)		
Mother HBIG injection				
Yes	1,324	1,265 (95.54)	1.256	0.557
No	591	551 (93.23)		
Delivery pattern				
Vaginal delivery	1,194	1,142 (95.64)	0.652	0.206
Cesarean delivery	1854	1807 (97.46)		
Feeding pattern				
Breast feeding	1,120	1,087 (97.05)	0.907	0.789
Formula feeding	1295	1238 (95.60)		
Neonate immunization				
Vaccine	265	224 (84.52)	0.427	0.027
Vaccine + HBIG	1,350	1,324 (98.07)		
Mother HBeAg				
Positive	1,415	1,346 (95.12)	0.090	<0.001
Negative	1,735	1,705 (98.25)		
Mother HBV DNA				
Positive	1,354	1,296 (96.36)	0.038	0.038
Negative	1,276	1,246 (97.64)		
Mother HBV DNA				
≥ 6 log10copies/ml	1,243	1,185 (95.33)	0.069	<0.001
< 6 log10copies/ml	1,387	1,357 (97.84)		

Table 2. — *Influencing factors of immune response to HBV vaccine and a meta-regression. Infants aged 8-12 months were enrolled in the follow-up study.*

Study author (reference)	Study country	Vaccine schedule	Final sample size	Anti HIV	Anti HCV
Zhang *et al.* [10]	China	Standard	539	0	0
Zhang *et al.* [3]	China	Standard	1150	0	0
Hwang et al. [11]	USA	Accelerated Standard	707	0	0
Ramasamy *et al.* [12]	Australia	Accelerated	73	0	0
Lugoboni *et al.* [13]	Italy	Standard	34	0	0

ministration, host factors (age, sex, race/ethnicity, education, BMI, smoking, alcohol, and drug use), study population seropositivity for antibody, and reported comorbidities. For studies reporting outcomes following standard and accelerated vaccination schedules, the data abstraction was divided into two parts to capture the details of each group, respectively.

Statistical analyses were done by use of Review Manager Version 5.0 software. Odds ratios (OR) and 95% confidence intervals (CI) were determined by use of a Mantel-Haenszel random-effects model shown in forest plots. For all tests done, a *p*-value of less than 0.05 was considered statistically significant. Heterogeneity of the outcome across studies was tested using Q-statistic (α= 0.01). Seroprotection estimates and their standard errors were converted into logits. Logits were used in order to avoid overestimation of heterogeneity, to take advantage of a normal distribution, and to achieve a stable variance analysis. Following this, meta-regression analysis was conducted to identify possible sources of heterogeneity.

Results

Search selection from the original and the updated electronic search, 911 unique citations including 847 specific to drug using populations were identified. Further screening revealed five potentially relevant articles, thus a total of five articles were chosen for this review (details of screening procedure displayed in Figure 1).

Study participant characteristics are detailed in Table 1. The publication years of the articles spanned from 2004 to 2014. In all studies, passive and active immunization-within 24 hours of delivery, 100 IU hepatitis B immunoglobulin (HBIG) and a dose of 10 mg HBV (at intervals of 0, 1, and 6 months) by intramuscular injection at different injection sites was given to neonates born to HBsAg positive mothers. All studies reported baseline data

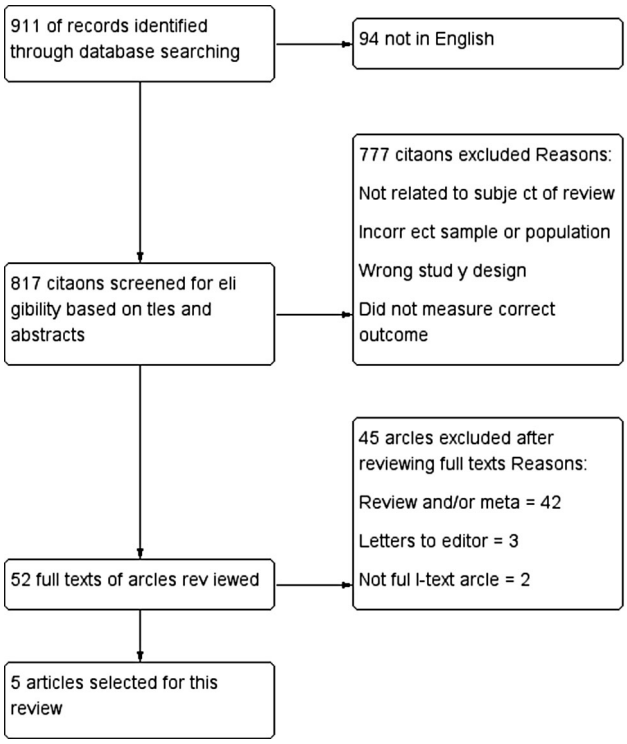

Figure 1. — The flow diagram of the study selection.

on anti-HIV, anti-HCV, and anti-HBc serological status of their participants.

In infants aged 7–15 months and infants aged 16–24 months, anti-HBs positive rate was 92.6% and 84.0% respectively. Results of bivariable analysis are provided in Table 2. In the group of HBeAg-positive mothers, anti-HBs positive rate in mother's age < 28 group was significantly lower than that of ≥ 28 group, and as well as in the vaccine-only versus vaccine plus HBIG group. Also, whether HBIG injection or not in the infants also influenced the anti-HBs positive rate. Among the infants whose mothers had their HBV DNA tested, HBV infected infants were all from HBV DNA-positive mothers whose HBV DNA were all ≥ 6 $\log_{10}$copies/ml. The anti-HBs positive rate was significantly lower in the positive mothers' infants. The quantity of HBV DNA objectively reflects the HBV replication levels in the host (Figure 2).

The funnel plot is reported in Figure 3. No inferential evidence of publication bias was detected.

No significant effect by the study design was detected by the meta-regression. Moreover, the age at vaccination and the time interval between vaccination and antibody titer assay did not appear to influence effect size.

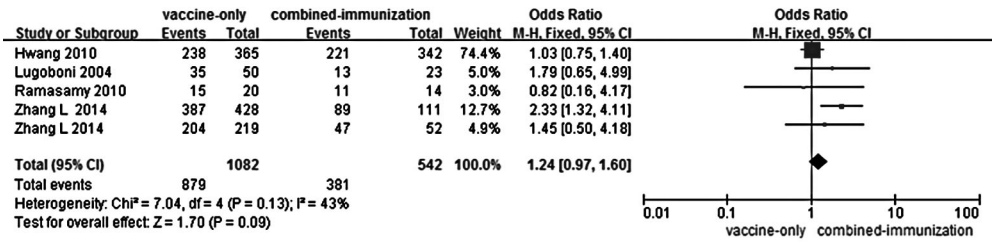

Figure 2. — Forest plot showing the outcomes between the vaccine-only and combined-immunization group by age 8–12 months.

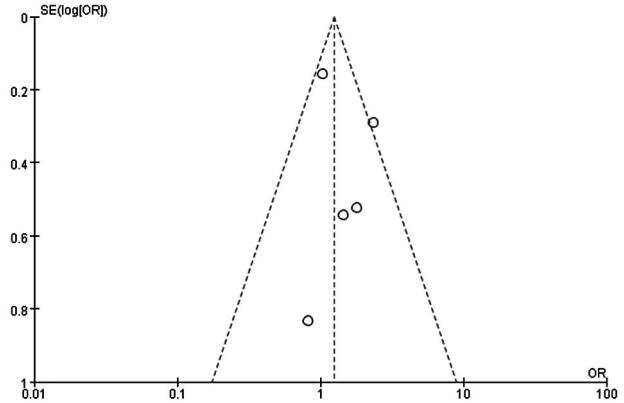

Figure 3. — Funnel plot showing the sensitivity analysis

Discussion

Without any intervention, infants born to HBsAg positive mothers have approximately a 40% chance of acquiring perinatal HBV infection. Immunization with HB vaccine and HBIG can prevent development of the persistent carrier state in at least 95% of infants born to HBeAg-positive mothers [14]. Although the immunoprophylaxis can prevent most of the development of the carrier status in infants born to HBsAg-positive mothers, this cannot totally be prevented. Therefore mother-to-infant transmission has been the major reason for chronic HBV infection for quite some time.

In summary, the present meta-analysis provides strong evidence that HBIG along with HB vaccine injection beginning after birth is effective and safe in the interruption

of HBV intrauterine infection and MTCT in HBV carrier mothers. Also, the authors applied meta-regression models to investigate influencing factors of immune response to HBV vaccine. The results revealed that mothers' age lower than 28 years was a factor of the immune response of the infants to HB vaccine. Also, whether HBIG injection was given or not in the infants also influenced the anti-HBs positive rate. Among the infants whose mothers had their HBV DNA tested, HBV infected infants were all from HBV DNA-positive mothers whose HBV DNA were all ≥ 6 $\log_{10}$copies/ml. Also, the anti-HBs positive rate was significantly lower in the positive mothers' infants. The quantity of HBV DNA objectively reflects the HBV replication levels in the host. Reports have shown that the higher the HBV DNA replication levels, the more infectious are the mothers. It is indicated that the failure of HBV immunoprophylaxis is significantly associated with maternal HBV DNA replication levels [8]. To identify those infants at high risk of HBV immunoprophylaxis failure, maternal HBeAg and HBV DNA need to be assessed prior to childbirth. The infants receiving vaccine only born to HBeAg and HBsAg positive mothers are more vulnerable to HBV infection compared with those receiving vaccine plus HBIG; however, no HBsAg positive was observed in infants born to HBeAg negative mothers in vaccine-only group or vaccine plus HBIG group, which may indicate it is unnecessary to receive HBIG in those infants.

These data can help facilitate the healthcare strategy, such as HBsAg-carrier women should be suggested to avoid pregnancy when HBV is of high replication in their bodies at younger age, or an antiviral should be routinely administered to pregnant woman to lower their viral load if necessary. So for asymptomatic HBV carrier mothers, the present authors also recommend HBIG and HB vaccine administration as an immune prophylaxis in their newborns, beginning after birth.

Some limitations of this meta-analysis, however, need to be acknowledged. First of all, the authors could include only observational cohort studies in this review, since randomized controlled trials were lacking. Observational studies may lack the experimental element of a random allocation to an intervention, nevertheless they can be regarded as a useful tool in order to assess the effectiveness of an intervention in a community, as opposed to the special setting of controlled trials.

Conclusion

Data from follow-up analysis of seven large randomized cohorts show that administration of HBIG and HB vaccines as an immune prophylaxis in infants born to HBV carrier mothers, beginning after birth, is effective in conditioning MTCT and immune response.

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